SOME ASPECTS OF THE CHEMISTRY OF 1,3,4-THIADIAZOLIUM SALTS AND RELATED COMPOUNDS

by

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ABSTRACT

The work described in this thesis has been divided into seven sections. The first section involves the preparation of N'-acyl-N'-aryl-N-benzothiohydrazides by the acylation of N'-aryl-N-benzothiohydrazides and is followed by a brief discussion of their possible conformation in solution.

The second section deals with the preparation of 1,3,4-thiadiazolium salts by the action of perchloric acid/acetic anhydride on N'-acyl-N'-aryl-N-benzothiohydrazides and also by the reaction of N'-aryl-N-benzothiohydrazides with nitriles in an acidic medium. The preparation of 2-methylthio-1,3,4-thiadiazolium methosulfate by methylating the corresponding thione is also described.

The third section deals with the reaction of 2-phenyl- and 2-methyl-1,3,4-thiadiazolium salts with alcohols in the presence of base. The stability and spectra of these compounds are discussed. Treatment of the 2-methyl-1,3,4-thiadiazolium salt with base was found to give rise to a dimeric anhydrobase and evidence supporting its structure is given. The anhydrobase could be trapped by a variety of acylating and thioacylating agents before dimerization occurred.

In the fourth section, the reaction of N'-acyl-N'-aryl-N-benzothiohydrazides with a variety of acid anhydrides is described. These compounds were found to be identical with those obtained by acylating

the anhydrobase. The mass spectral fragmentation of these compounds is described and the anomolous product obtained upon thiobenzoylation of 3-methyl-1-phenyl-pyrazal-5-one is also discussed.

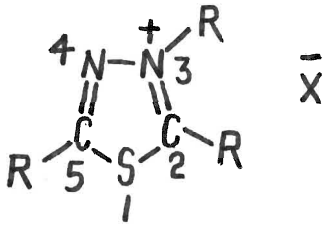
The fifth section deals with thioacyl derivatives of the anhydrobase which were prepared by the action of phosphorus pentasulfide upon the oxygen analogues and also obtained as the major product of the reaction of thioacetic acid with compounds related to N'-aryl-N-benzothiohydrazides. The mass spectra and p.m.r. spectra of these compounds are discussed.

In the sixth section, the reaction of the 2-methylthio-1,3,4-thiadiazolium salt with active methylene compounds to give acyl and diacyl derivatives of the anhydrobase is described. Some aspects of these compounds are discussed.

The seventh section describes the synthesis of "cyanine" type dyes incorporating the 1,3,4-thiadiazole ring and their spectra are briefly discussed.

I N T R O D U C T I O N

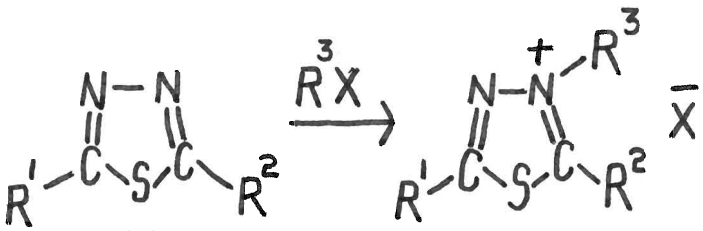
The work in this thesis is mainly concerned with 1,3,4-thiadiazolium salts (1) and closely related compounds.



(1)

I. PREPARATION OF 1,3,4-THIADIAZOLIUM SALTS

Previously, these salts were prepared by the alkylation of the corresponding thiadiazole (2). This restricted the types of



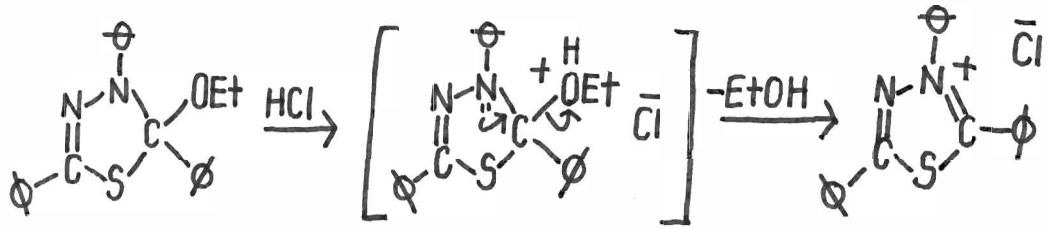
(2)

$X=I,\ R^1=R^2=R^3=CH_3$, ref 1

$X=I,\ R^1=R^3=CH_3,\ R^2=SCH_3$, ref 2

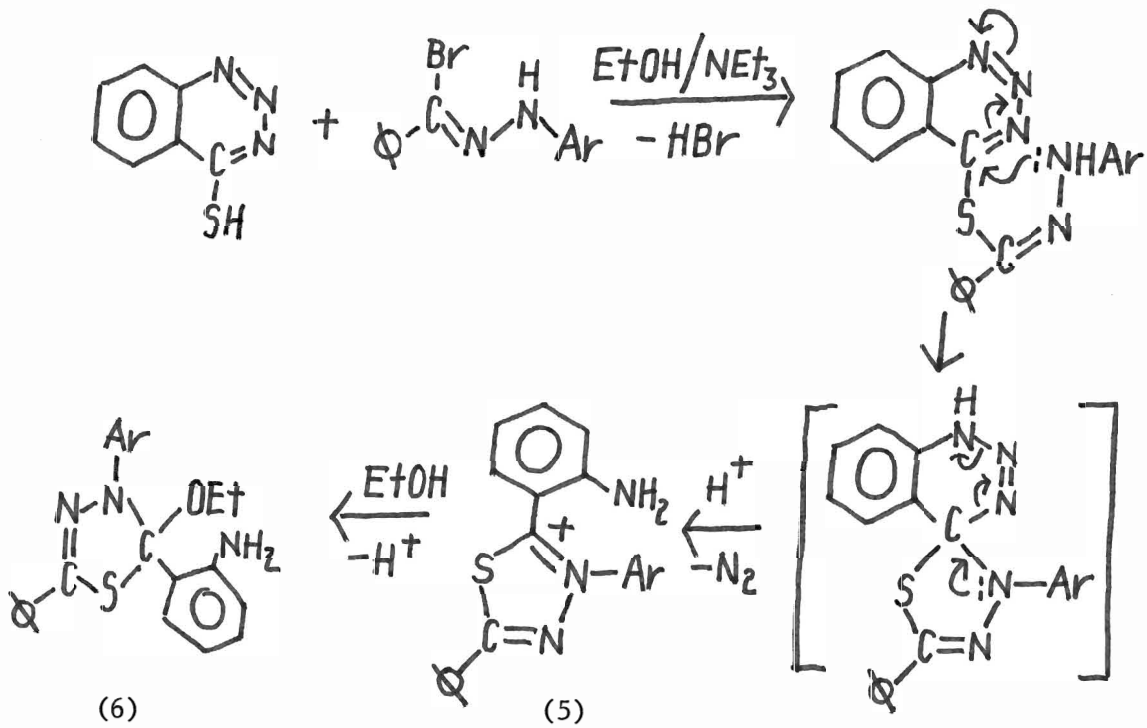
thiadiazolium salts available to those containing an alkyl group in the 3 position.

The only exceptions found were the triphenyl salt[3] (3), prepared



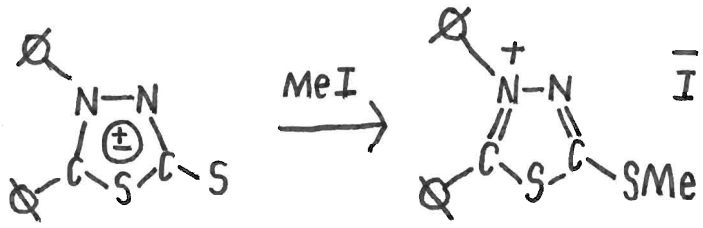
(4) (3)

by the action of hydrogen chloride upon the ethyl ether (4), the triaryl ion[4] (5), isolated as the ethyl ether (6), and the salt (7)



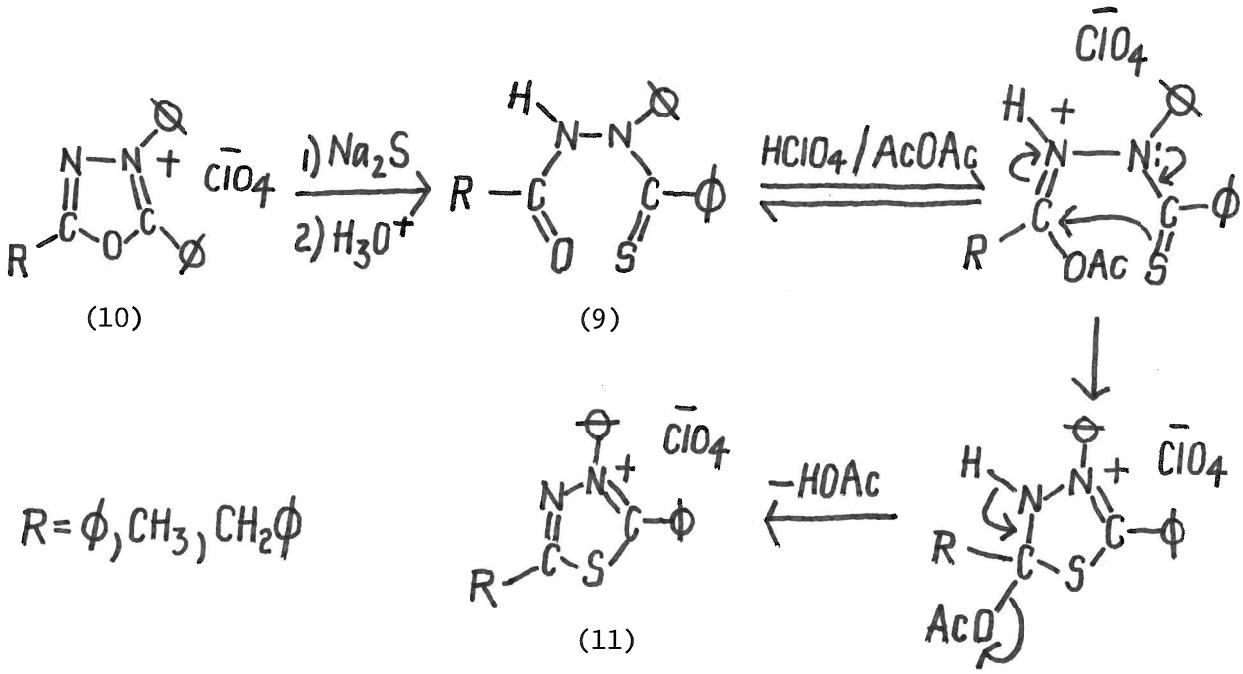
(6) (5)

prepared by the alkylation of the mesoionic thiadiazole (8).



(8) (7)

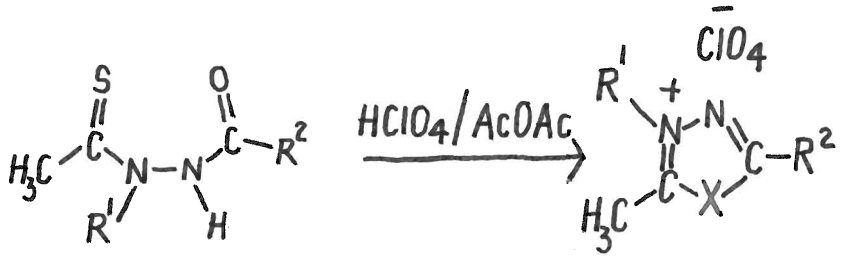
However, Boyd and Summers[6] found a new route to these salts which promises to allow much greater scope in the nature of the substituents, particularly aryl, attached to the ring. They showed that certain acyl thiohydrazides (9), obtained by the ring opening of 1,3,4-oxadiazolium salts (10) with aqueous sodium sulfide, cyclized in



(10) (9) (11)

the presence of acetic anhydride/perchloric acid to give thiadiazolium salts (11).

Other acyl thiohydrazides (12) under these conditions reverted to the original oxadiazolium salts or gave a mixture of the two salts.



(12) (13)

(a) $R^1=R^2=\phi$, $X=O$

(b) $R^1=\phi$, $R_2=CH_3$, $X=O$

(c) $R^1=p\text{-}NO_2\phi$, $R_2=CH_3$, X, $O:S=2:1$

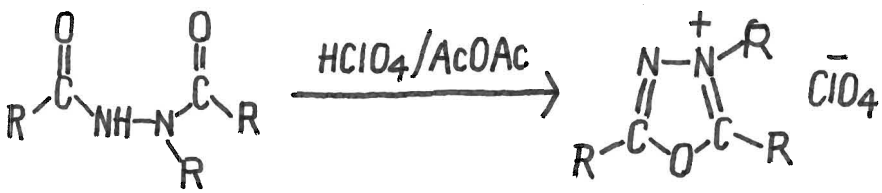
It was thought that the electron withdrawing effect of the phenyl group in the thiobenzoyl compounds (9) favored acetylation of the oxygen atom and hence the formation of (11); whereas the electron releasing methyl group in the thioacetyl derivatives directed acetylation to sulfur, so that (13) was produced. In the case of (13c), the electron withdrawing effect of the p-nitrophenyl substituent directed some of the acetylation away from the sulphur atom.

II. REACTIONS OF 1,3,4-THIADIAZOLIUM SALTS

Relatively little of the chemistry of thiadiazolium salts had been examined. The work which has been done is largely based upon the detailed study undertaken by Boyd and his coworkers of the

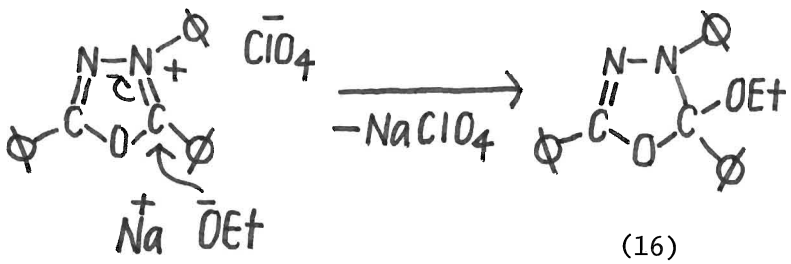
reactions of 1,3,4-oxadiazolium salts. In view of the broad scope of this work and the close parallel that exists between the two ring systems, it will be discussed in some detail.

These salts (14), prepared by the cyclization of diacyl hydrazines (15) with perchloric acid/acetic anhydride,



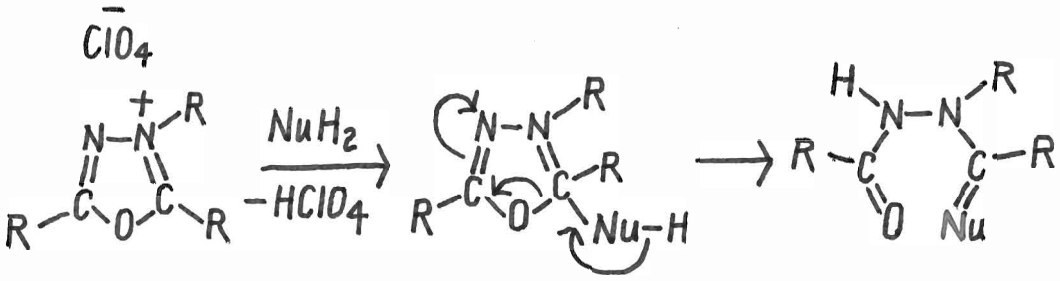
(15) (14)

were subjected to a wide variety of nucleophiles and it was found that attack occurred at the 2-position as exemplified by the reaction with alkoxide ion to give the ethyl ether[8] (16).



(16)

If the nucleophile could lose a proton, the primary adduct (17) underwent ring opening to give the substituted hydrazide (18).

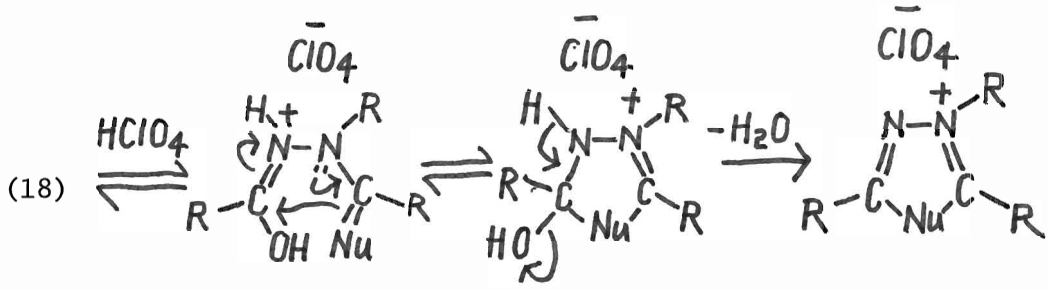


(17) (18)

NuH_2 = H_2O, H_2S,  , H_2N-R, active methylene compounds

These hydrazides were found to be relatively unstable in acid or basic media and their subsequent recyclizations are of two mechanistic types.

The first involves cyclization such that one atom of the nucleophile (19), or the original oxygen (20), is incorporated into the ring. In this way oxadiazolium salts could be transformed, via the substituted acyl hydrazide, into 1,3,4-thiadiazolium salts (19) (NuH_2 = H_2S),[6]



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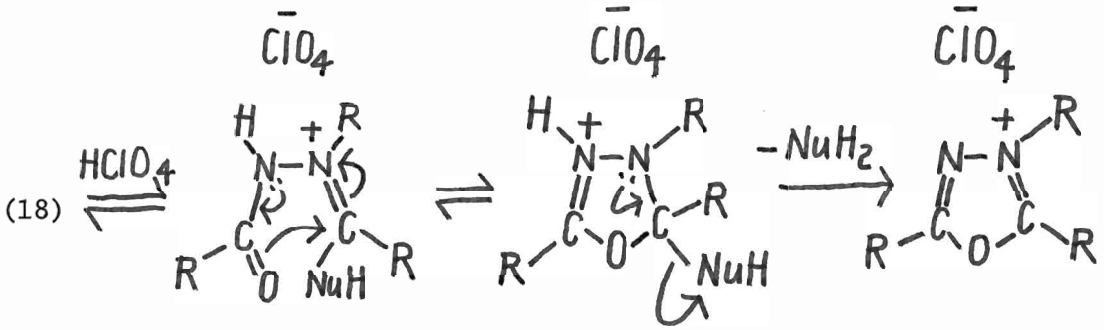
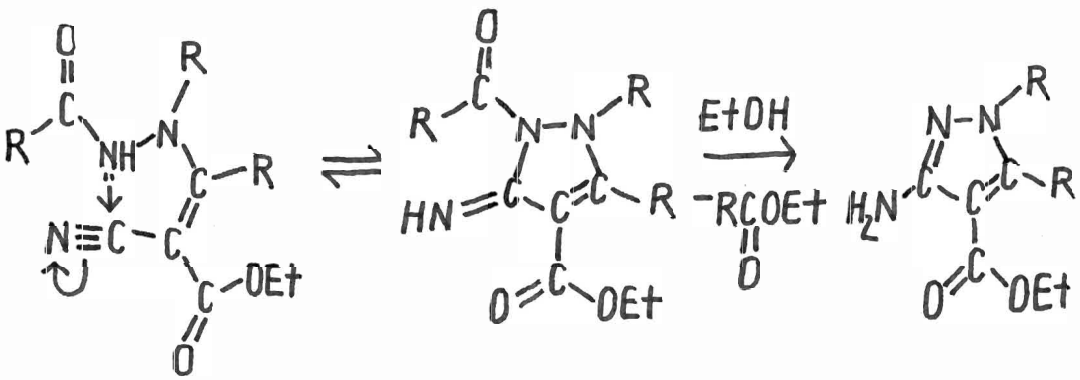


(18)

(20)

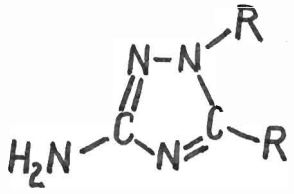
1,2,4-triazolium salts (19) (NuH_2 = NH_2-ϕ)[9] or back into the original oxadiazolium salts (20) (NuH_2 = H_2S).[6]

In the second type of mechanism, the nitrogen adjacent to the carbonyl group initiates the cyclization so that two atoms of the nucleophile are incorporated in the new ring. This is typified by the case when the ring opening nucleophile is ethyl cyanoacetate[10] (21). Through this route, oxadiazolium salts were transformed into



(21) (22)

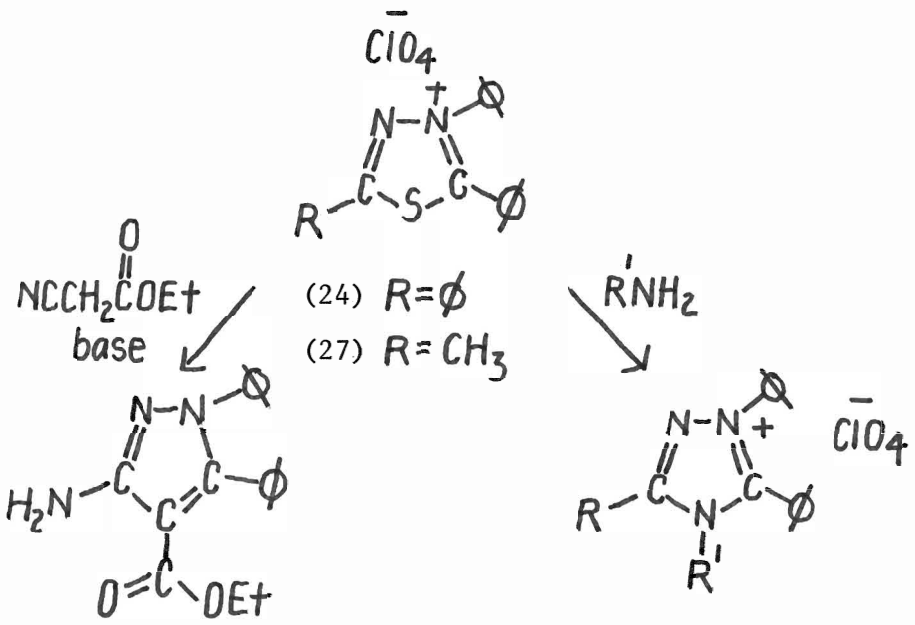
pyrazoles (22) and triazoles[11] (23) (NuH_2 = cyanamide).



(23)

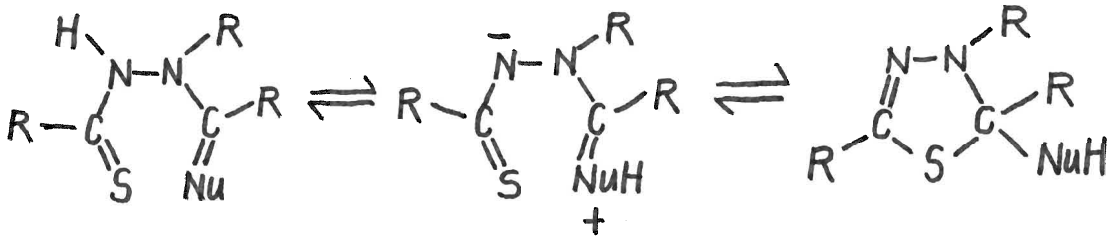
1,3,4-Thiadiazolium salts were found to behave similarly with respect to nucleophiles[12] although somewhat more vigorous reaction conditions were required and lower yields were obtained.

The thiadiazolium salt (24) gave triazoles (25) on treatment with amines and the pyrazole (26) with ethyl cyanoacetate.



(26) (25)

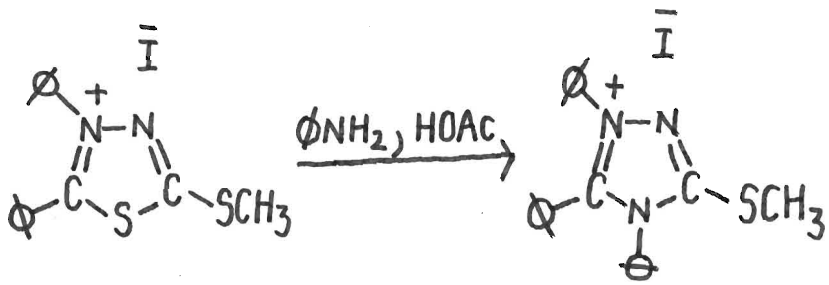
However, the other salt (27) although reacting with the active methylene compound to give (26) would not react with amines. Presumably, the greater nucleophilicity of sulfur shifts the equilibrium between (28) and (29) further towards the right, making subsequent recyclization to a new ring more difficult. In the case of (27), the electron



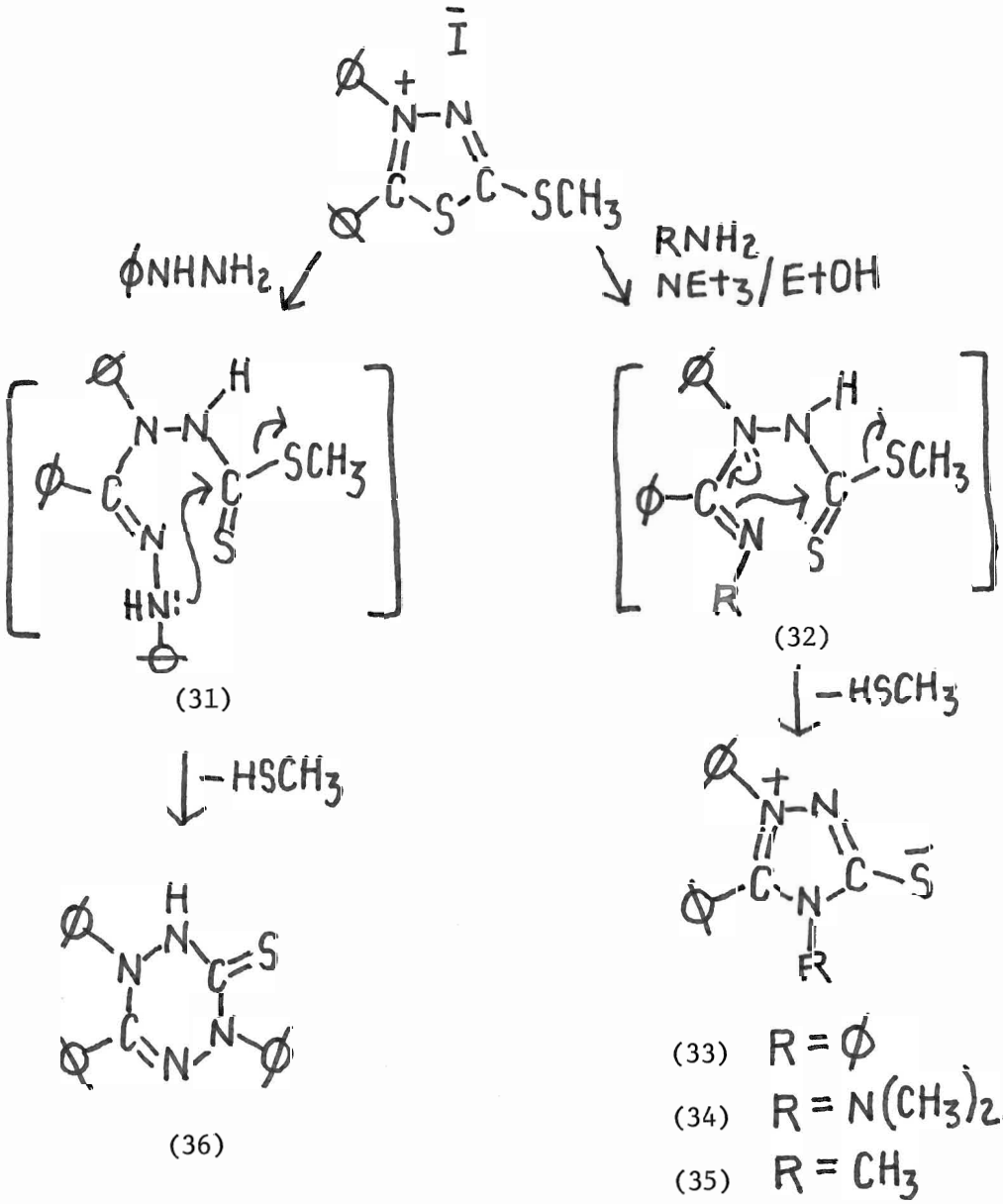
(28) (29)

releasing nature of the methyl group, relative to that of the phenyl group, makes cyclization to the triazole (25) impossible.

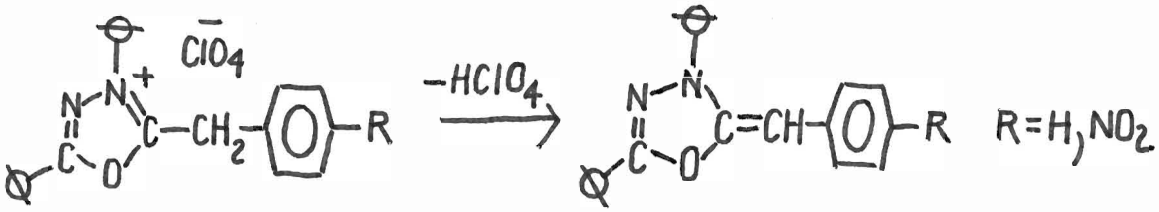
The salt (7) exhibited a similar reactivity in an acidic medium, giving the triazole[13] (30) on reaction with aniline. However, under basic conditions, displacement of the thiomethyl group from the ring opened intermediates (31) and (32), resulted in the formation of mesionic triazoles (33)[13], (34)[16] and (35)[5] or tetrazines (36).[15]



(7) (30)

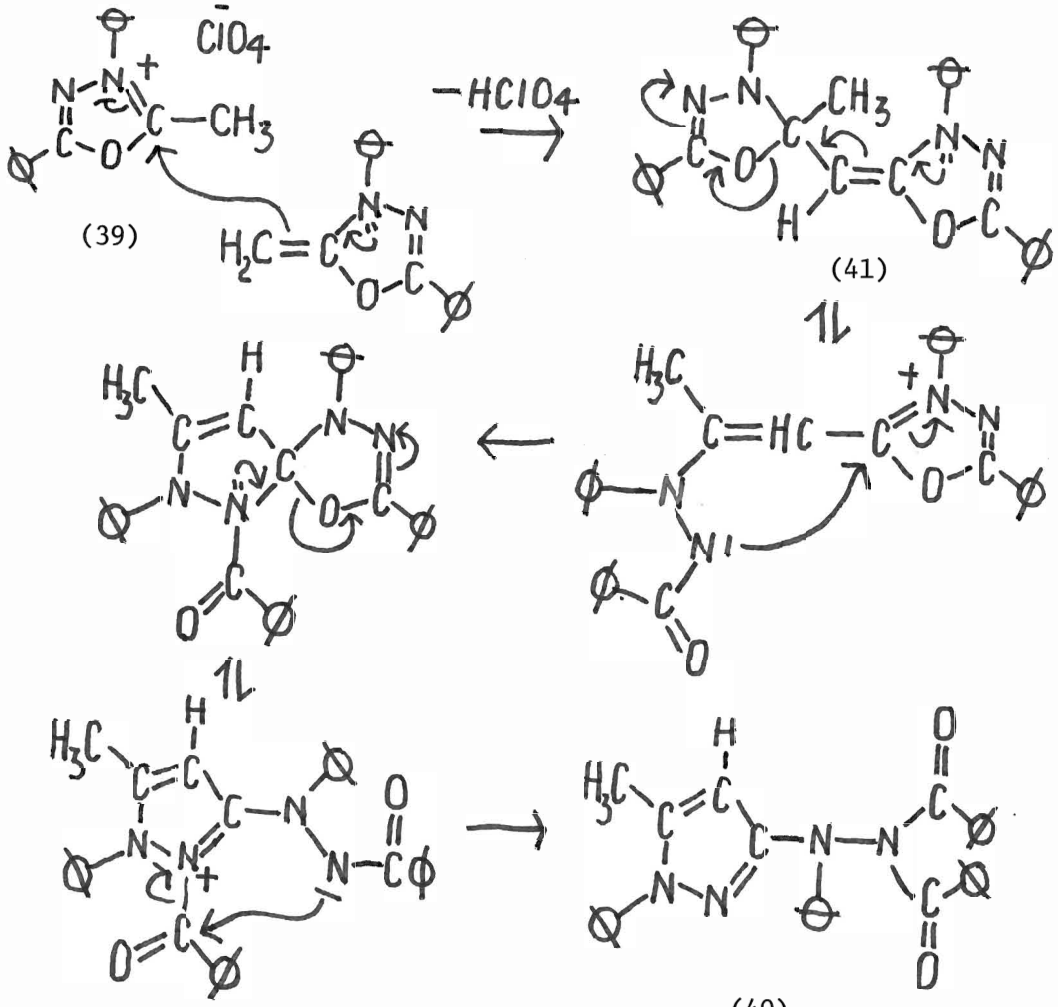

I⁻
ϕNHNH2
RNH2
NEt3/EtOH
SCH3
HN
R
(31)
(32)
-HSCH3
-HSCH3
(33) R = ϕ
(34) R = N(CH3)2
(35) R = CH3
(36)

Boyd and Dando[15] also showed that 2-benzyl-oxadiazolium salts (37) could be deprotonated with base to give the corresponding anhydrobases (38). The 2-methyl salt (39) was thought to dimerize



(37) (38)

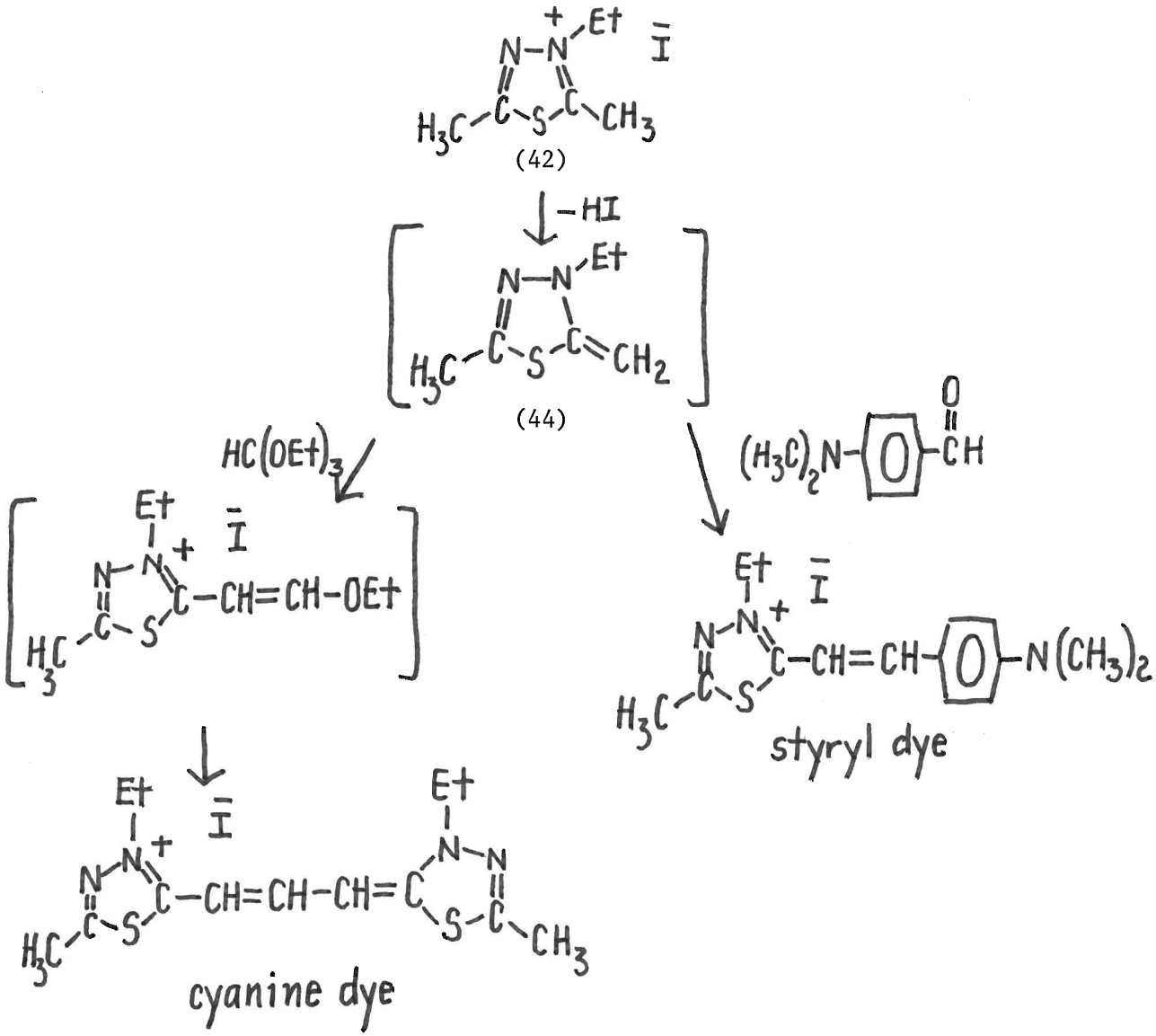
first and then further rearrange to give the observed pyrazole (40).

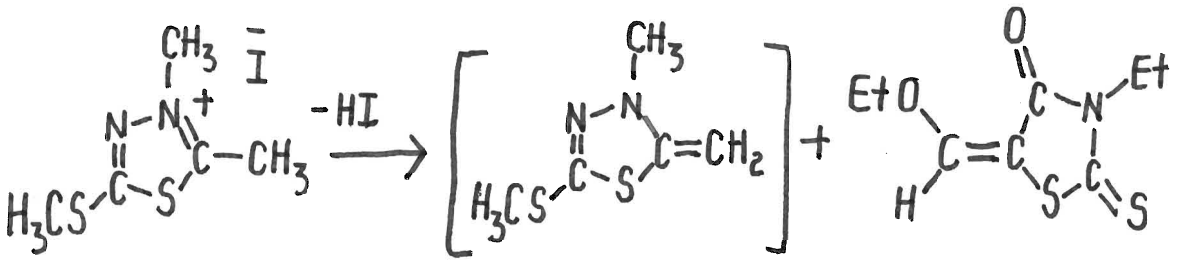


(39) (41)

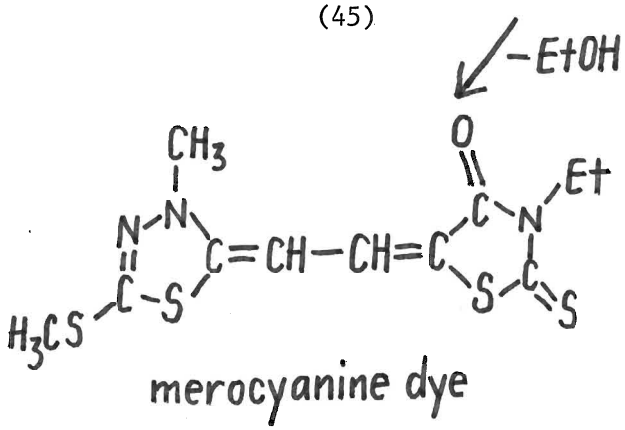
(40)

Most of the early chemistry of thiadiazolium salts involved the transformation of the 2-methyl analogue, for example (42) and (43), into merocyanine,[16] styryl[17] and cyanine[17] type dyes, it being found that they were useful as sensitizers of photographic silver halide emulsions.[16] These reactions would involve analogous anhydrobase intermediates, (44) and (45).



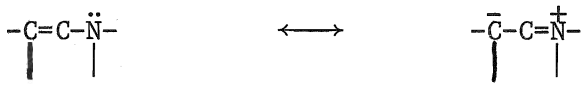


(43) (45)



merocyanine dye

The anhydrobase is really a specific example of an enamine, a term first introduced by Wittig and Blumenthal[18] to describe the nitrogen analogues of enols. The electron pair on nitrogen overlaps with the π electrons of the double bond giving a system which can be regarded as a resonance hybrid of the two canonical forms (46) and (47). It is, therefore, capable of reacting with electrophiles through both

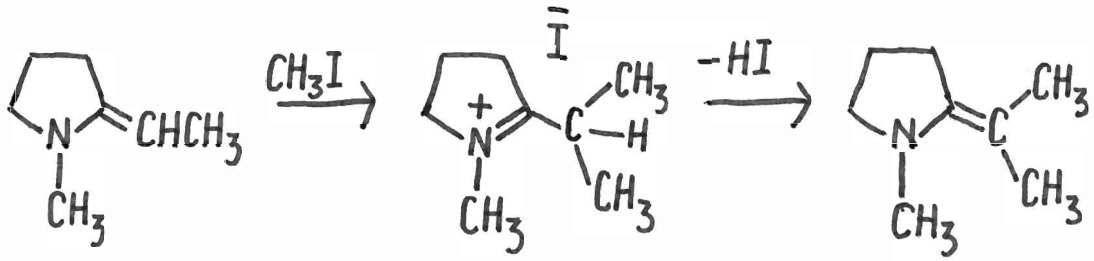


(46) (47)

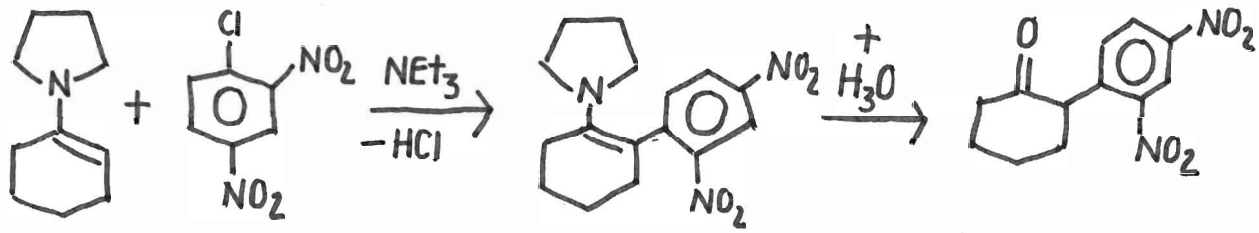
nitrogen or carbon, although it is the latter that most often predominates, especially in the case of tertiary enamines.

Some examples of the reactivity of enamines[19] would include:

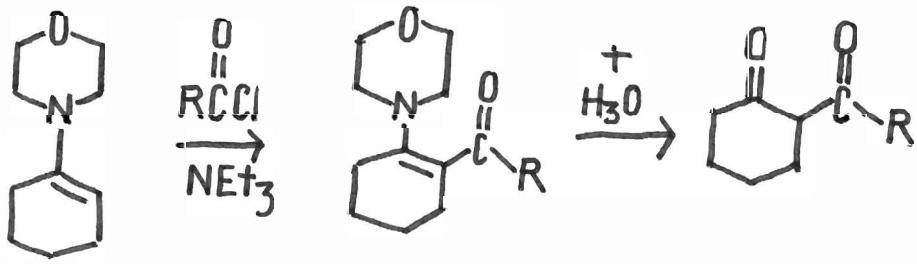
(a) alkylation



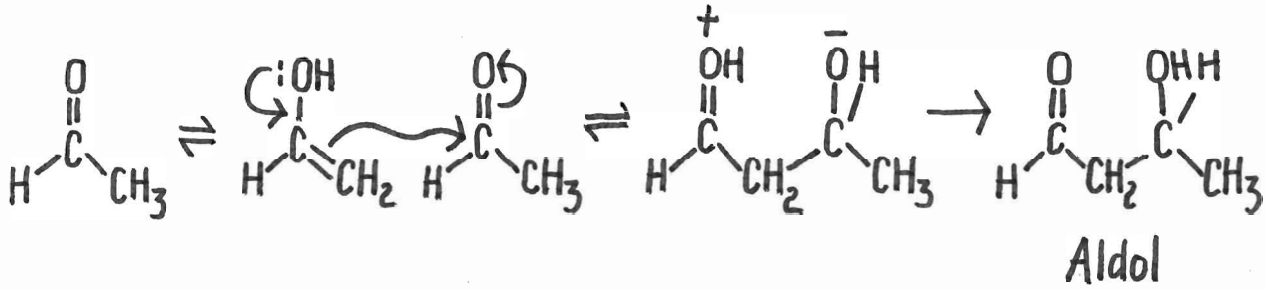
(b) arylation

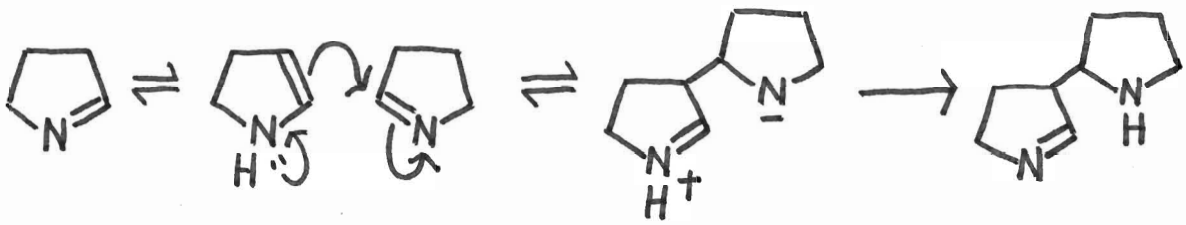


(c) acylation



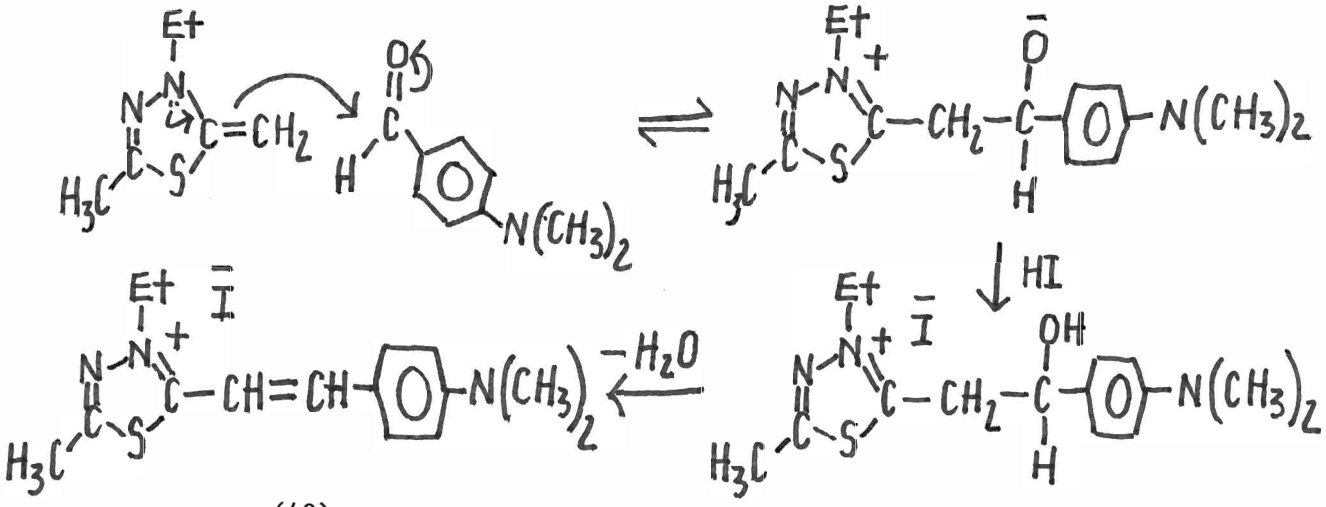
Many enamines exist as dimers, either through the reaction of the enamine with its conjugate acid, as in the formation of Boyd intermediate (41) or through auto-condensation[20] (48). The latter is an aldol type of reaction and many of the reactions of enamines, such as





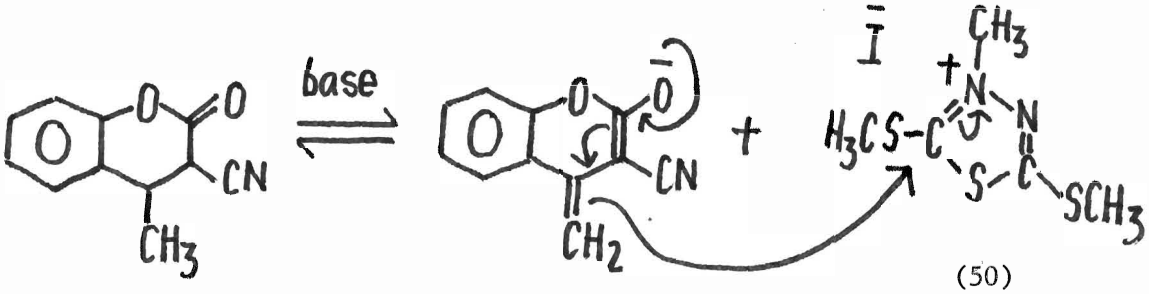
(48)

the formation of (49), may be regarded as mixed aldol condensations.



(49)

Another aspect of the chemistry of thiadiazolium salts involves those salts containing a potential leaving group in the two position. The 2-thiomethyl derivatives (50) and (51) have been used to prepare the merocyanine dye[21] (52) and the 2-acylamino derivative[2] (53).



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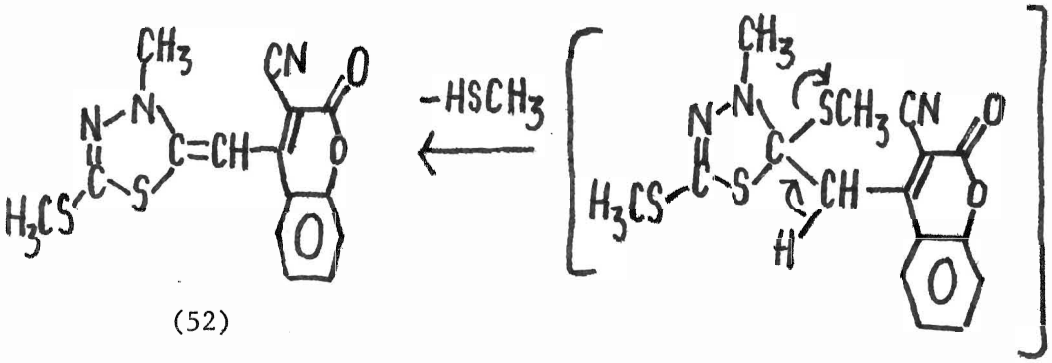

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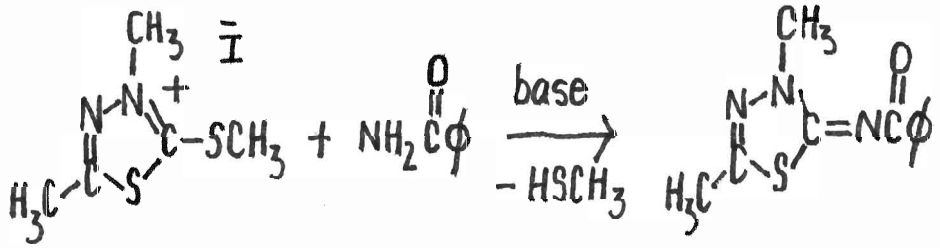
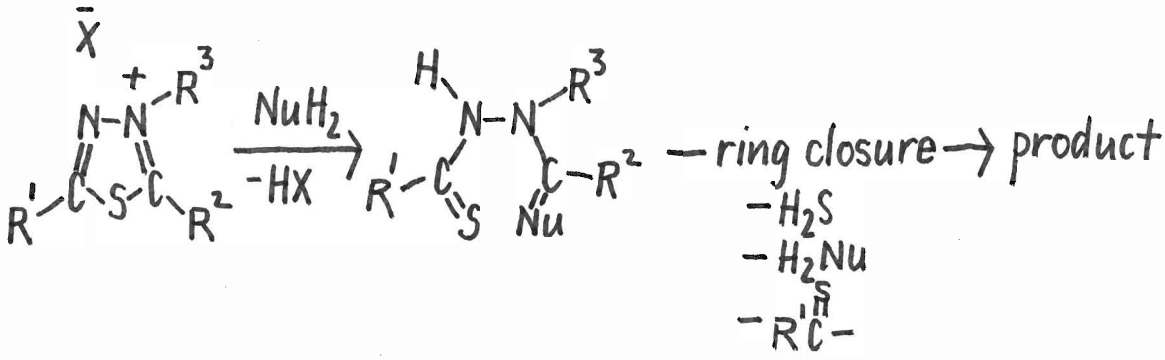


(51) (53)

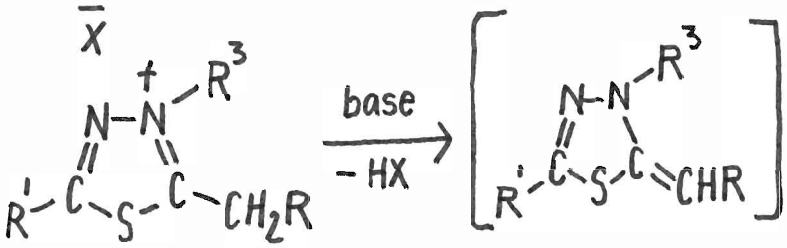
The reactions of 1,3,4-thiadiazolium salts can, therefore, be divided into three categories, according to the nature of the 2-substituent.

(a) R^2 = aryl



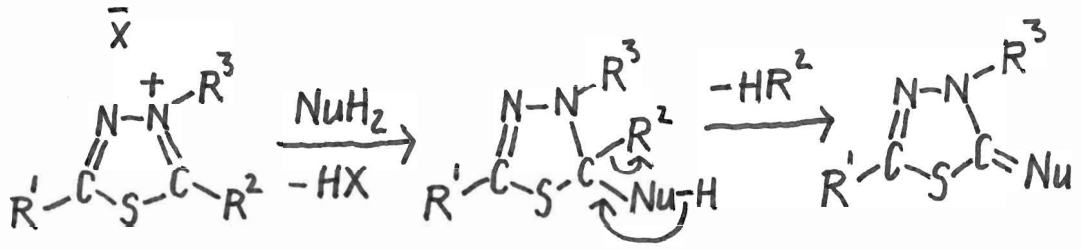
The common feature of this group of reactions would involve the formation of the substituted benzothiohydrazide which then closes to give the original thiadiazolium salt or a new heterocyclic ring. A subgroup of this category would be the case when R^1 is a potential leaving group such as a thiomethyl function. In this instance, mesionic triazoles or tetrazines are formed.

(b) R^2 = alkyl with acidic protons



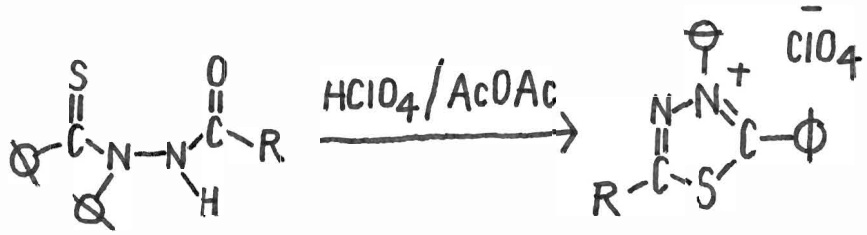
In this case, the intermediate anhydrobase formed reacts as an enamine.

(c) R^2 = SMe or some leaving group



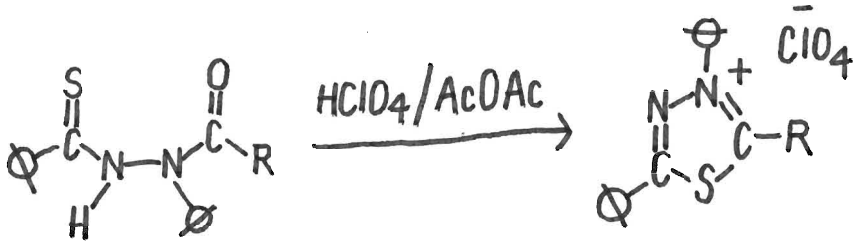
In this instance, thiadiazolines with exocyclic double bonds are formed.

As previously mentioned, Boyd and coworkers prepared thiadiazolium salts by the ring closure of acyl benzothiohydrazides of the type (9). In these salts, the phenyl group is in the reactive 2- position



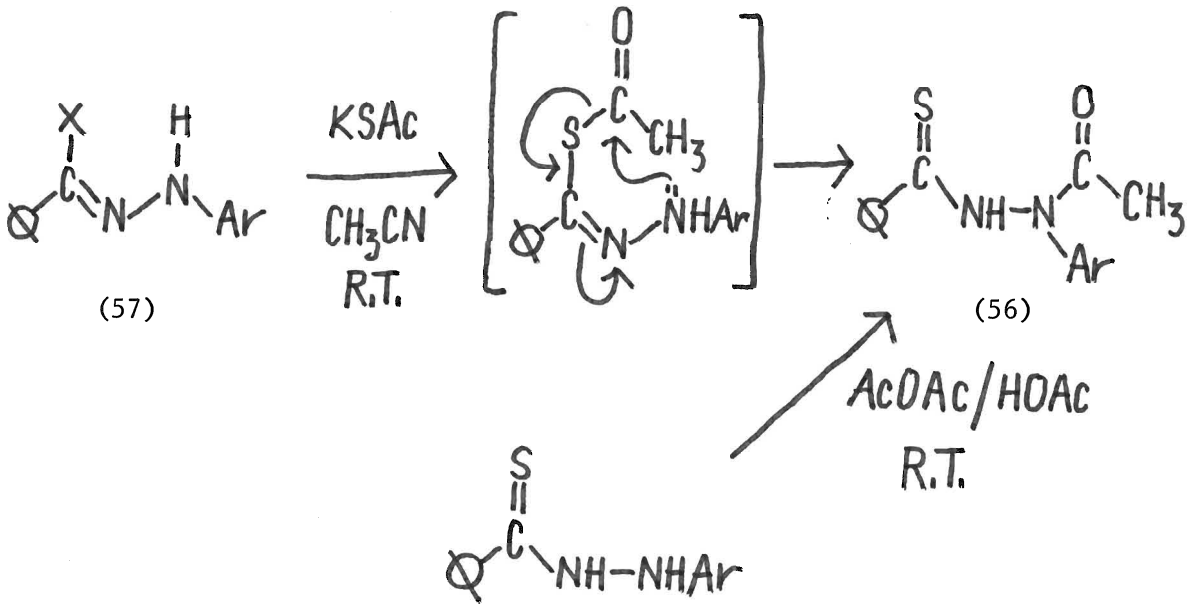
(9)

because the nitrogen adjacent to the thiocarbonyl group is substituted. If, however, the nitrogen adjacent to the carbonyl group were substituted, as in (54), ring closure would give salts of the type (55) and thereby allow for the preparation of 2-alkyl-3,5-diarylthiadiazolium salts.



(54) (55)

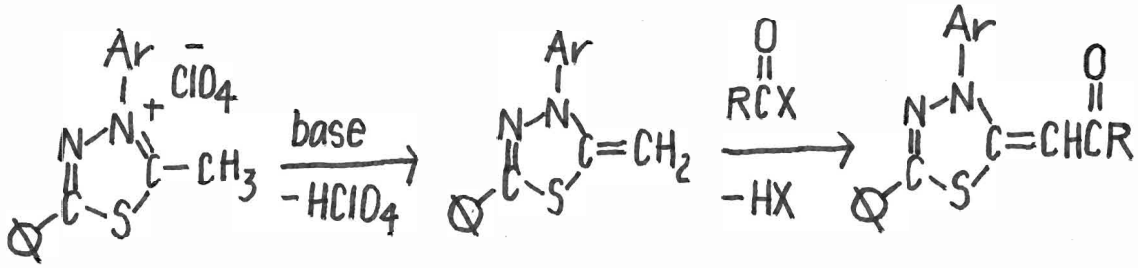
Gibson and coworkers[22,23] have prepared benzothiohydrazides of this type (56) by the reaction of potassium thioacetate with hydrazonyl halides (57) and by the acetylation of benzothiohydrazides (58).



(57) (56)

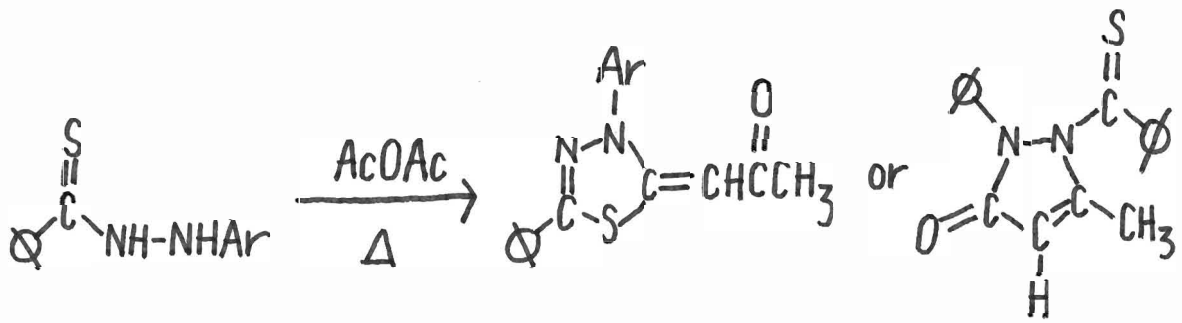
(58)

In the work described in this thesis, acylbenzothiohydrazides (56) will be examined as potential sources of thiadiazolium salts and some aspects of the chemistry of these salts, along with that of the 2-thiomethyl analogue, will be investigated. Particular attention will be focussed on possible acyl- derivatives (59) of the anhydrobase



(59)

since these were thought to result from the reaction of acetic anhydride with benzothiohydrazides[24,25] although Barton and coworkers[26] have proposed an alternate structure (60).



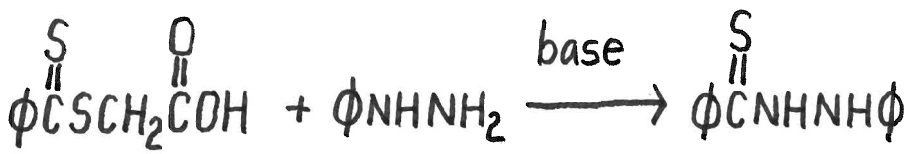
(60)

D I S C U S S I O N

1. PREPARATION OF N'-ACYLBENZYLTHIOHYDRAZIDES

As mentioned in the introduction, Gibson and coworkers[22,23] have prepared N'-acetylbenzothiohydrazides by the reaction of hydrazonyl halides with potassium thioacetate and by acetylating benzothiohydrazides. In this work, the latter approach was used since it would allow for the preparation of a variety of N'-acylbenzylthiohydrazides by using different acylating agents.

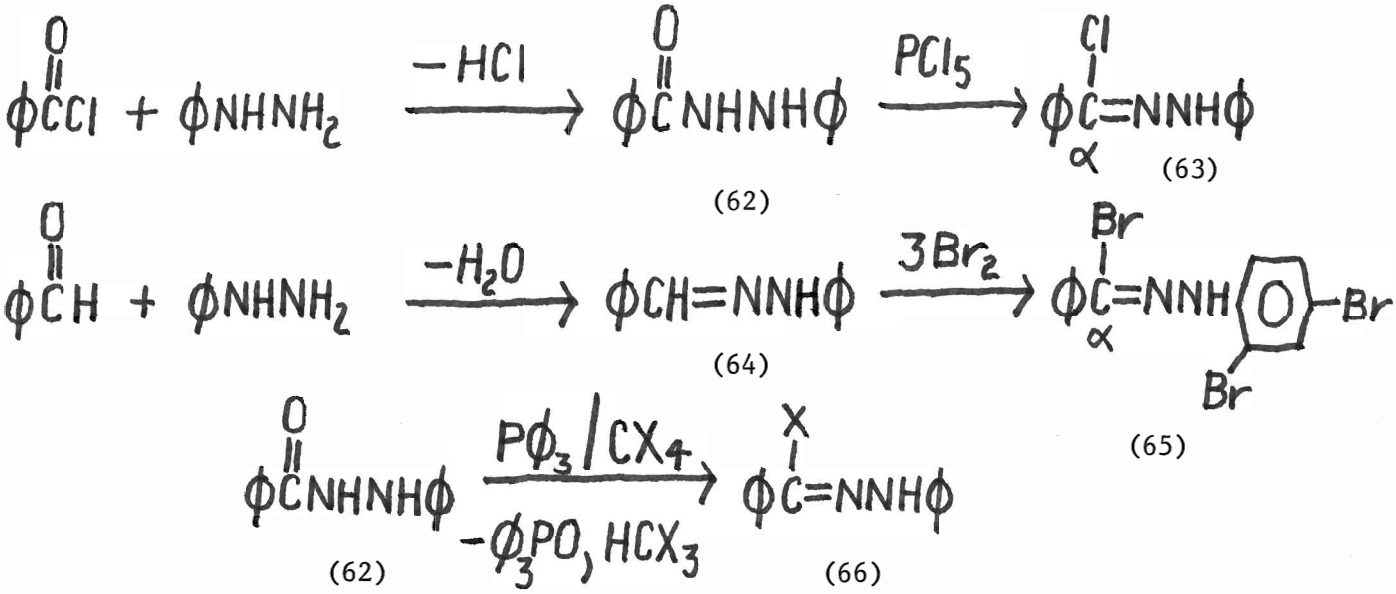
Benzothiohydrazides are generally prepared by two different methods. The first involves the reaction of an arylhydrazine with thiobenzoylating agents[27] such as thiobenzoylthioglycolic acid (61).



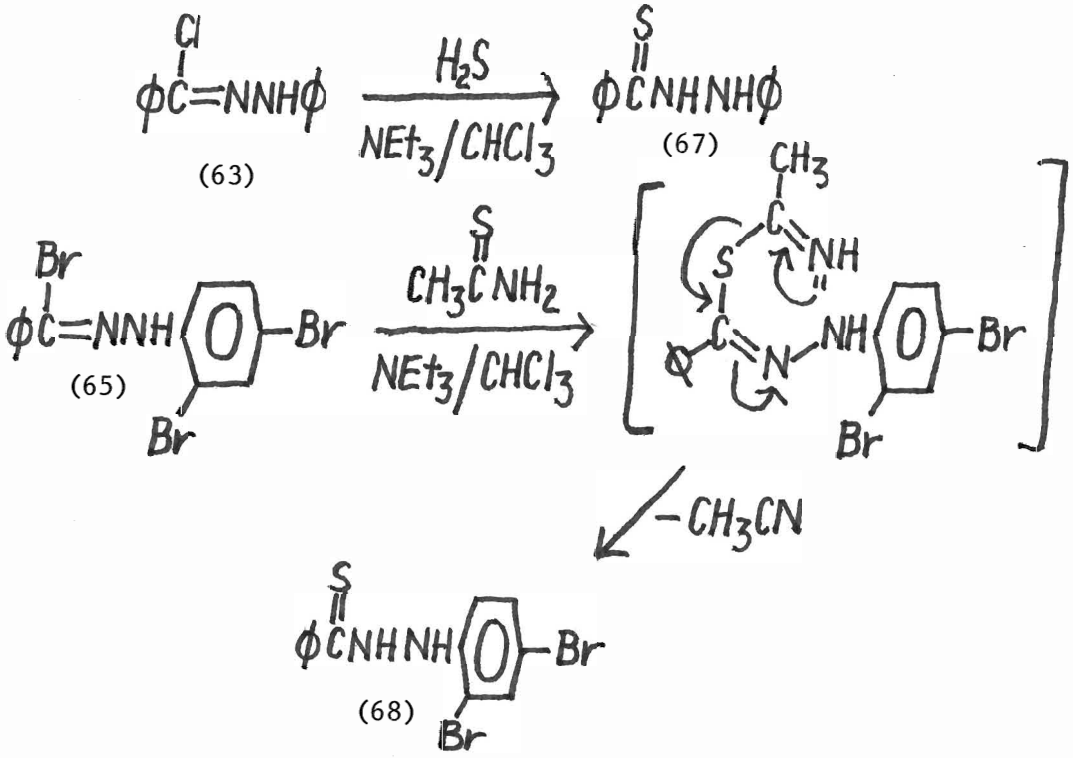
(61)

In the other approach, which was used in this work, a hydrazonyl halide is reacted with a sulphur containing nucleophile. Hydrazonyl halides are commonly prepared by the reaction of aroyl phenylhydrazides (62) with phosphorus pentachloride[28] or of a halogen with N'arylidenephenylhydrazones[29] (64). A recent method involves the reaction of hydrazides (62) with triphenyl phosphine/carbon tetrahalide to give the hydrazonyl halide (66). The α-halogen in these compounds behaves

similarly to the halogen in an acyl halide and can be displaced by

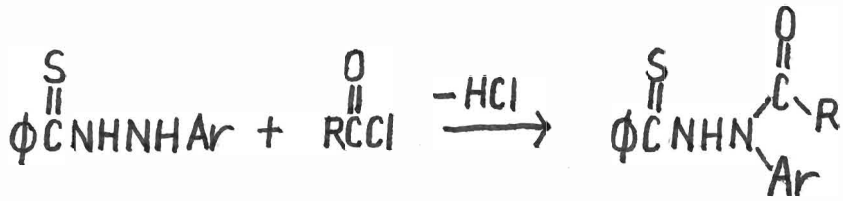


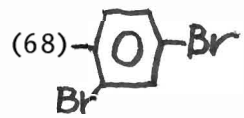
sulphur to give the benzothiohydrazide. In this way, the thiohydrazides (67) and (68) were prepared by reacting the hydrazonyl halides (63) and (65) with hydrogen sulfide[31] and thioacetamide[32] respectively under basic conditions.



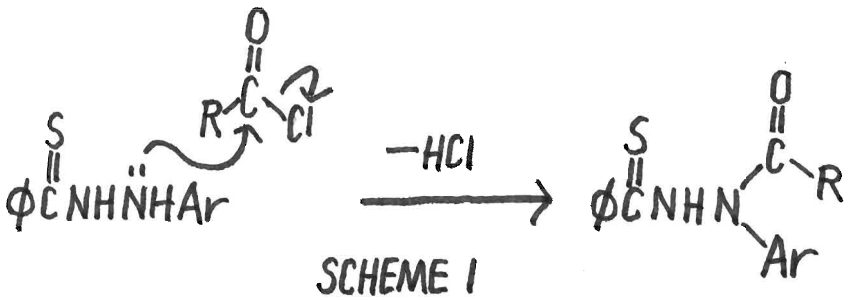
The benzothiohydrazides (67) and (68) were then acylated with various acyl chlorides. Pyridine was used as the solvent and hydrogen chloride scavenger in the case of aliphatic acyl chlorides and aqueous sodium hydroxide (Schotten-Baumann conditions) when benzoyl chloride was used. The results of the reactions are recorded in Table 1.

TABLE 1

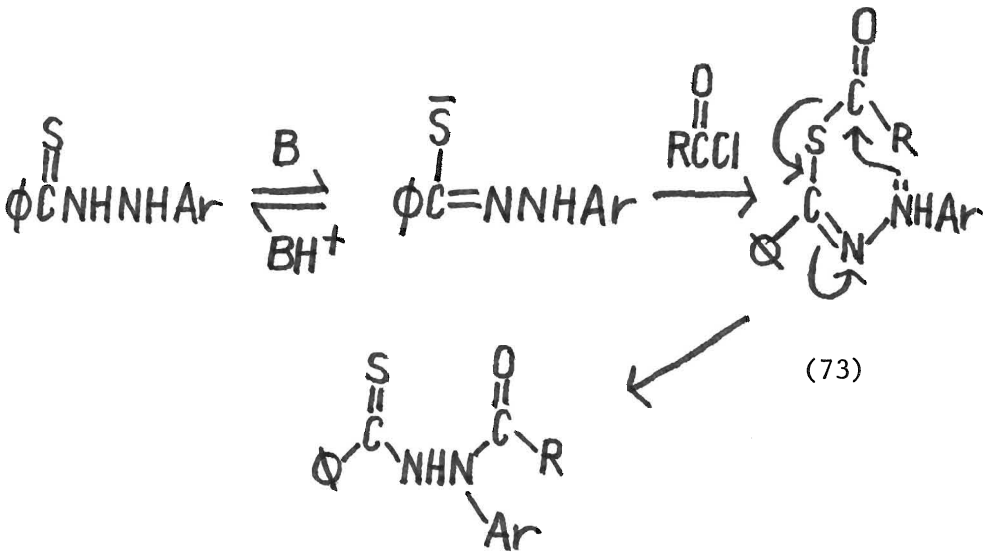


	Ar	R		yield	m.p.°
(68)		CH_3	(69)	78%	176-178 (lit., 177-178)[25]
(68)	"	CH_3CH_2	(70)	94%	150-154
(68)	"	ϕ	(71)	75%	127-129
(67)	ϕ	CH_3	(72)	79%	147-150 (lit., 154)[33]

The mechanism of these reactions is uncertain. They could proceed directly through N-acetylation (scheme 1) or S-acetylation followed by an S to N acyl transfer (scheme 2) could occur.



SCHEME 1



(73)

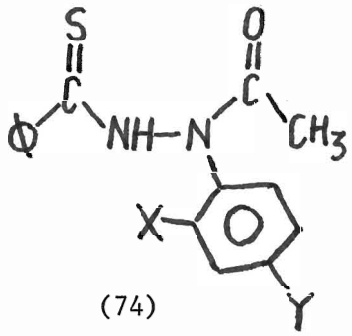
SCHEME 2

The S-acetyl intermediate (73) was proposed in the reactions of hydrazonyl halides with potassium thioacetate which gave N'-acyl-benzothiohydrazides.[34] Although they could not be isolated, they were thought to undergo a Smiles type of rearrangement to give the observed product.

Two of these compounds, (69) and (72), had already been prepared and the present samples were found to have identical spectral properties with those reported. It was however, difficult to match the melting points since these compounds began to decompose before the

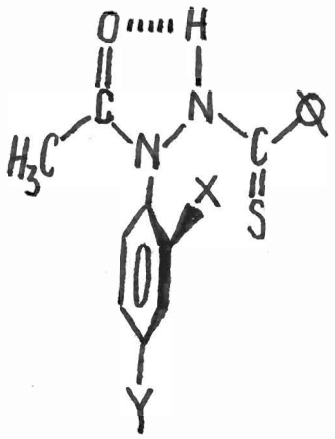
melting point was reached. The mass spectra of these compounds show a very weak molecular ion and a more intense ion corresponding to the loss of •OH or water[23]. This would suggest that these compounds thermally lose water when heated.

The p.m.r. spectra of these compounds is somewhat unusual as noted by Callaghan[23] who examined the spectra of a wide variety of N'-acetyl-N'-aryl-benzothiohydrazides (74). It was found that when the X substituent was Cl, Br or I, the methyl and N-H signals appeared as doublets. The addition of deuterium oxide caused the NH absorptions to disappear while the methyl absorptions remained unaffected.



(74)

When X = Y = H or X = I, Y = F, the methyl protons existed as a singlet and the NH proton was buried in the aromatic region. In the case of X = Y = F, splitting of the methyl protons was observed but it was difficult to ascertain the position of the NH absorption. A tentative explanation was suggested involving a hydrogen bonded structure (75) where restricted rotation about the N-aryl bond was brought about by the presence of bulky substitutents such as Cl, Br or I in the ortho position.



(75)

It was then stated that each methyl peak would be associated with one or the other of the N-H peaks in the two major conformers. The two major conformers referred to are presumably (75) and its mirror image but as to how this would induce a shift difference in the N-H or methyl protons is not readily apparent.

The data from the p.m.r. of the compounds prepared do not offer any conclusive explanations but will all the same be discussed.

The p.m.r. spectrum of the acetyl derivative (69) in deuterated dimethyl sulfoxide showed a similar spectrum to that run in deuterochloroform except that the doublet methyl peaks were no longer of equal intensity, the ratio of the upfield to the downfield signal being approximately 1:3. These signals were observed to coalesce at approximately 70°C, and appear to indicate that intramolecular hydrogen bonding may only be present in one of the isomers since the possibility of intermolecular hydrogen bonding with the solvent could bring about the observed reduction in the population of this conformer.

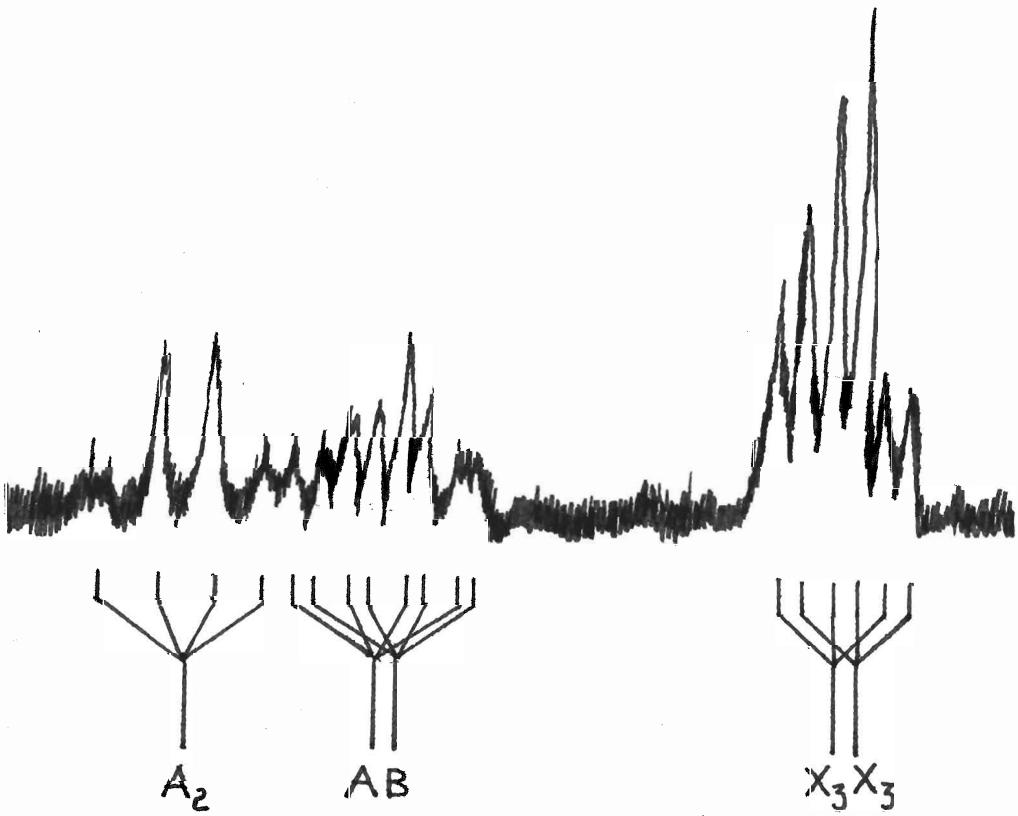
The unsubstituted acetyl benzothiohydrazide (72) showed a single methyl absorption at room temperature but, contrary to what Callaghan had reported, the N-H signal was observed as a broad adsorption, still recognizable as two peaks, centered at approximately 10.9 δ. In another spectrum run at ambient temperature, the N-H absorption appeared as an extremely broad peak centered at approximately 10.5 δ. When the sample was cooled to -50°C, the methyl resonances were slightly split (1.89 and 1.92 δ) and the N-H absorptions were observed as a sharp doublet (11.4 and 11.7 δ).

The benzoyl derivative (71) showed only a broad absorption for the N-H peak at 10 δ.

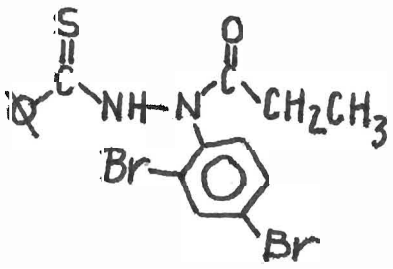
The propionyl derivative (70) showed a complex splitting pattern for the ethyl group (Figure 1). Decoupling the methyl groups gave two broad signals for the methylene absorptions with peak widths of approximately 9 Hz at half height. The N-H absorptions were again observed as a doublet (9.3 and 9.7 δ).

These data would suggest that there is a hydrogen bonded conformer present. This would be indicated by the solvent effect upon the methyl absorption in the acetyl derivative where the possibility of intermolecular hydrogen bonding appeared to bring about a reduction in the population of this conformer. It could even be argued that the structure of the hydrogen bonded form is (75) since the ethyl portion of the propionyl derivative appears to be an ABX_3 spin system superimposed upon an A_2X_3 spin system. The ethyl group in the hydrogen bonded conformer could be sensitive to the chiral center present or

FIGURE 1



Ethyl Portion of the p.m.r. Spectrum of

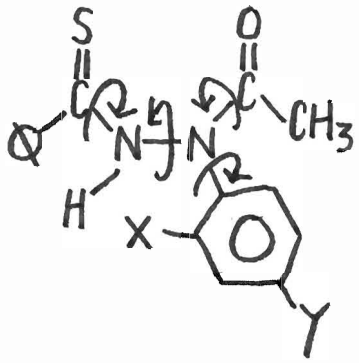


(70)

might experience restricted rotation due to the N-aryl group and appear as an ABX_3 spin system. In the decoupled spectrum the AB portion appeared as a broad absorption and could not be resolved into the expected doublet.

The data also suggest the presence of one or more non-hydrogen bonded conformers. The downfield methyl absorption which increased in size in deuterated dimethyl sulfoxide and the A_2X_3 part of the propionyl derivative could be attributed to them. There is also the apparent upfield shift of the N-H protons once they have coalesced as observed in the case of the acetyl derivative.

This is a fairly complicated problem since there are several possibilities of restricted rotation as shown for (76). There is the

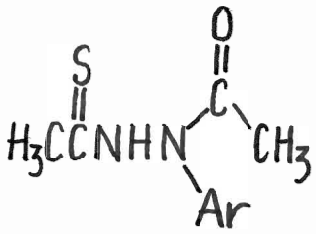


(76)

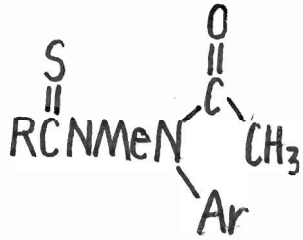
possibility of restricted rotation about the nitrogen-carbonyl[35] and nitrogen-thiocarbonyl[35] bonds, the N-aryl bond;[35] and the N-N bond.[36]

Further insight into this problem would require a more detailed study of this system. This would probably require the synthesis of other thiohydrazides such as (77) and (78) which could give some

indication of the importance of restricted rotation about the N-thiocarbonyl bond and hydrogen bonding. Ultimately, finding



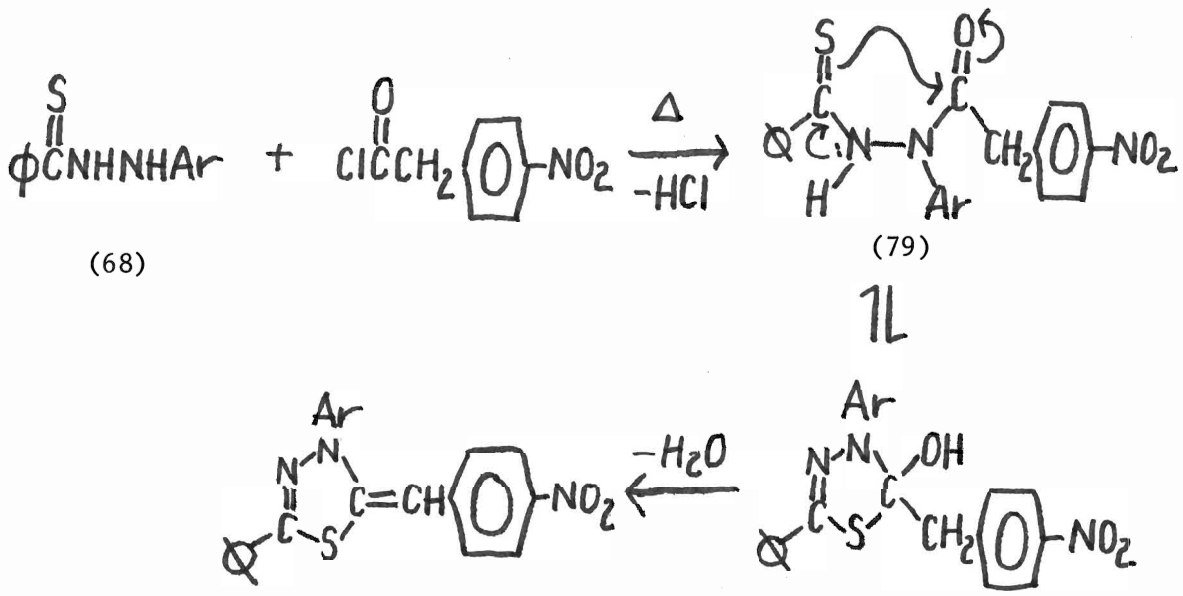
(77)



(78)

the magnitude of the energy barrier(s) for conversion between the conformers and comparing them with those known for simpler systems would perhaps show what is happening.

On attempting to prepare the p-nitrophenylacetylbenzothiohydrazide (79) an anomalous product was obtained. The benzothiohydrazide (68) was refluxed with an equivalent of p-nitrophenylacetyl chloride in dry benzene, the conditions which Boyd and coworkers[7] used to prepare the oxygen analogue of (79). However, the major product of the reaction was a red solid accompanied by unreacted benzothiohydrazide (t.l.c.). When two equivalents of the acid chloride were used, the formation of the red product was essentially complete. This material according to the elemental analysis, mass spectrum and the absence of a carbonyl stretch in the infrared spectrum appeared to be the anhydrobase (80). Unfortunately, because of its low solubility in organic solvents, a p.m.r. spectrum could not be obtained.



(68) (79)

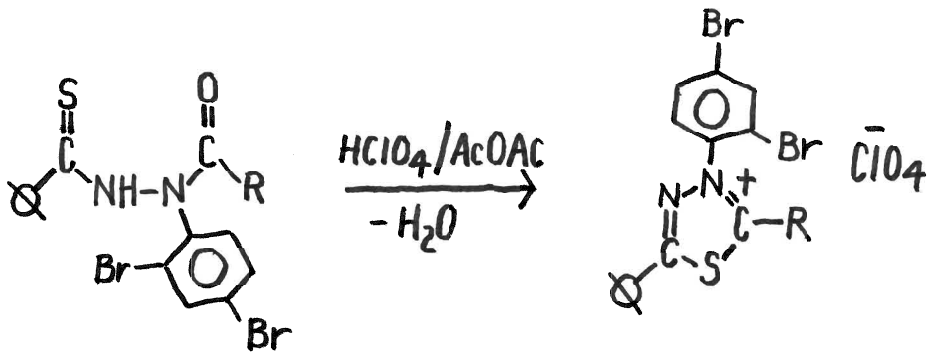
(80) (81)

Presumably, the greater nucleophilicity of sulphur relative to that of oxygen can bring about equilibration between (79) and (81). The acidity of the methylene protons in (81) combined with the presence of HCl and acid chloride could bring about the loss of water to give (80).

2. PREPARATION OF 1,3,4-THIADIAZOLIUM SALTS

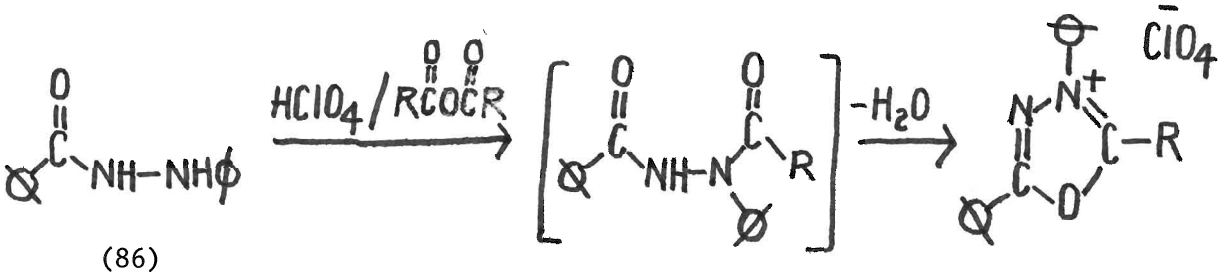
The salts (82), (83) and (84) were prepared from the N'-acyl-N'-aryl-benzothiohydrazides (69), (70), and (71) using the method of Boyd and Summers.[6] A suspension of the benzothiohydrazide in acetic anhydride was treated with perchloric acid and the thiadiazolium salt either precipitated or was induced to precipitate by the addition of ether. The results are summarized in Table 2.

TABLE 2



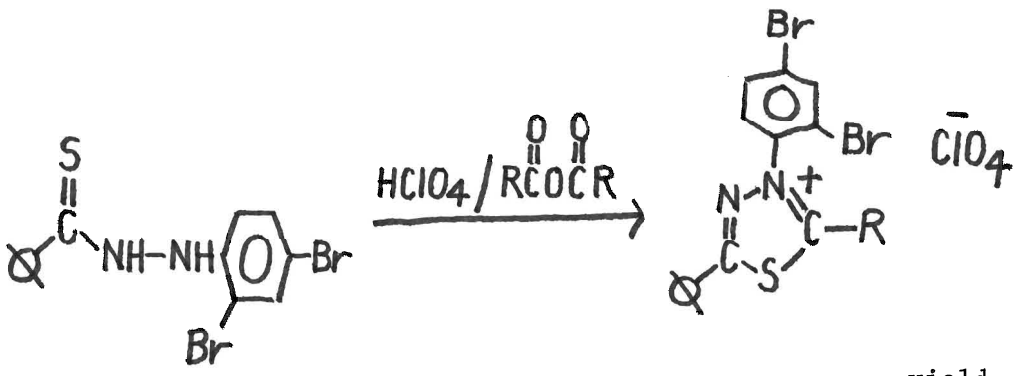
			yield
(69)	R = CH_3	(82)	88%
(70)	R = CH_2CH_3	(83)	94%
(71)	R = ϕ	(84)	86%

Boyd and Summers[7] have prepared analogous oxadiazolium salts (85) in one step by simultaneously acylating and cyclizing the hydrazide (86) with the desired acid anhydride and perchloric acid. The



(86) (85)

benzothiohydrazide (68) was found to behave similarly, giving the thiadiazolium salts (82) and (83) on treatment with acetic anhydride/perchloric acid and propionic anhydride/perchloric acid respectively.

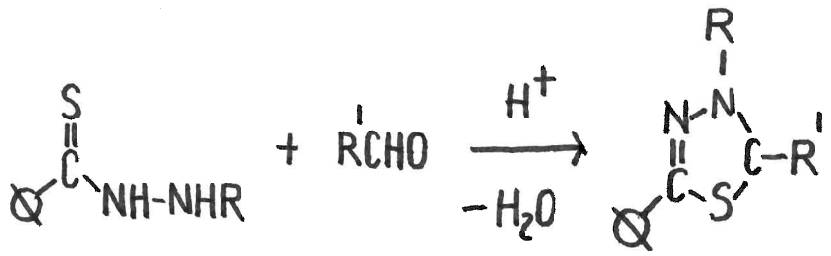


(68)

		yield
(82)	R = CH_3	86%
(83)	R = CH_2CH_3	94%

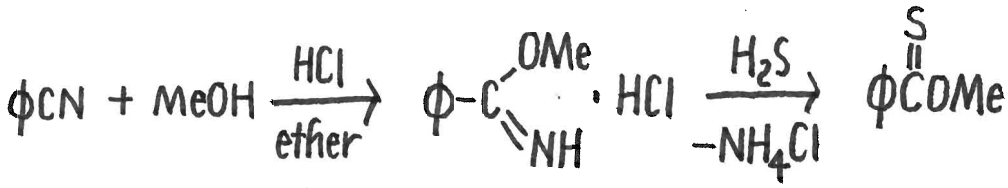
On considering other possible routes to these salts, it was thought that they could be obtained by reacting the benzothiohydrazide with a nitrile in the presence of perchloric acid. Benzothiohydrazides

have been shown to cyclize upon reaction with aldehydes to give thiadiazolines[37] (87). That nitriles could be similarly employed was

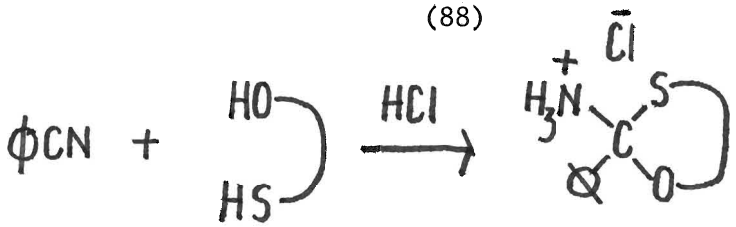


(87)

shown by Lawson and coworkers[38] who reacted benzonitrile with methanol in the presence of hydrogen chloride to obtain the salt (88). This upon treatment with hydrogen sulfide gave the thioester (89). Now



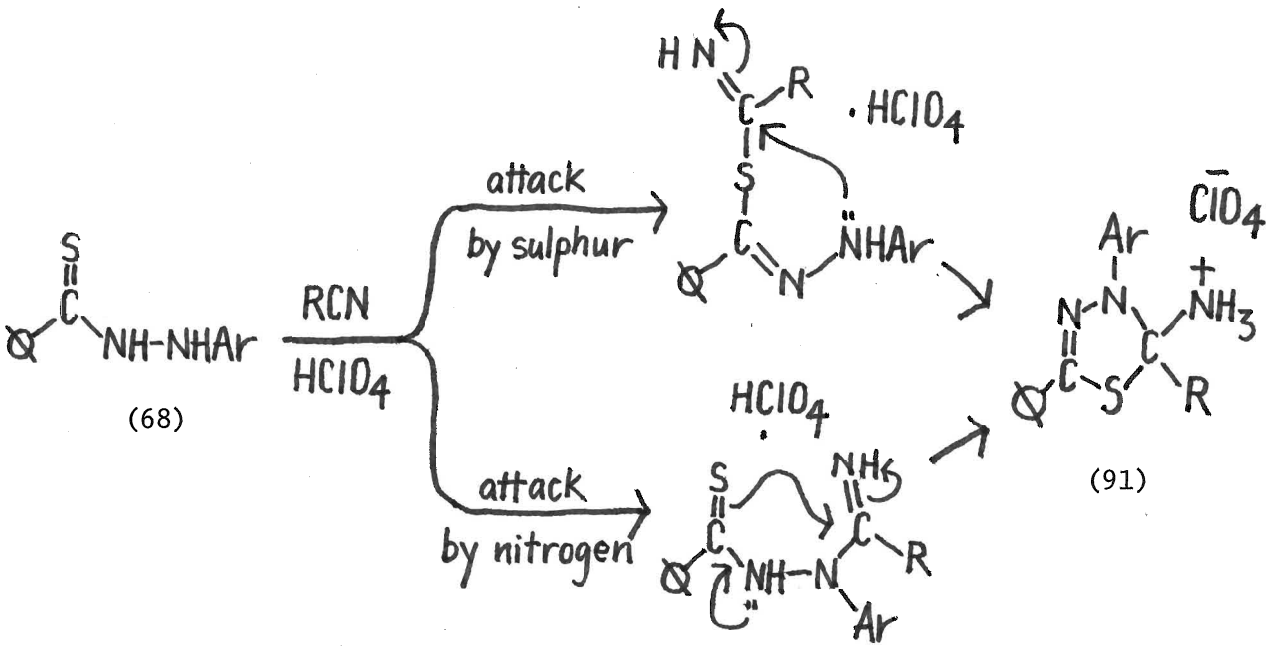
(88) (89)



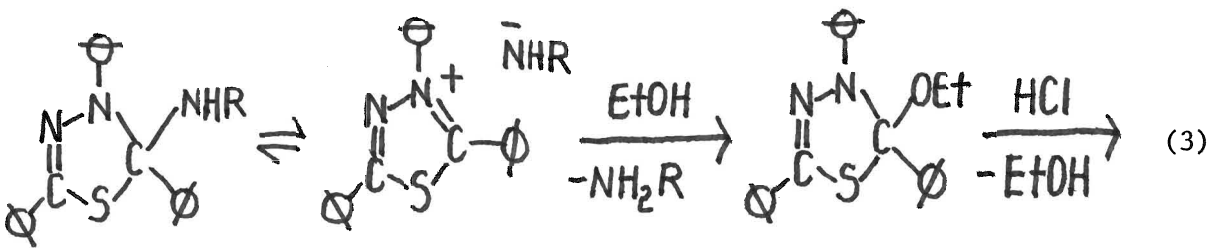
(90)

if the two nucleophiles were part of the same molecule, a salt like (90) could be formed.

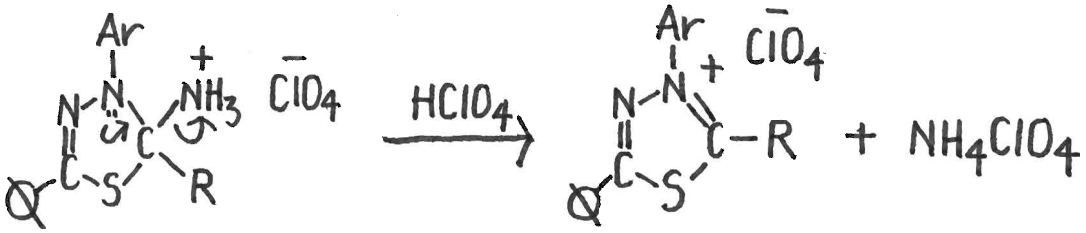
Applying this to the reaction under consideration, one would expect the perchlorate (91).



A species such as (91) would be expected to be quite unstable under these conditions since Huisgen and coworkers[3] showed that the amine (92) was converted to the ethyl ether (4) on attempted crystallization from ethanol. The ether in turn gave the thiadiazolium salt (3) on treatment with hydrogen chloride.



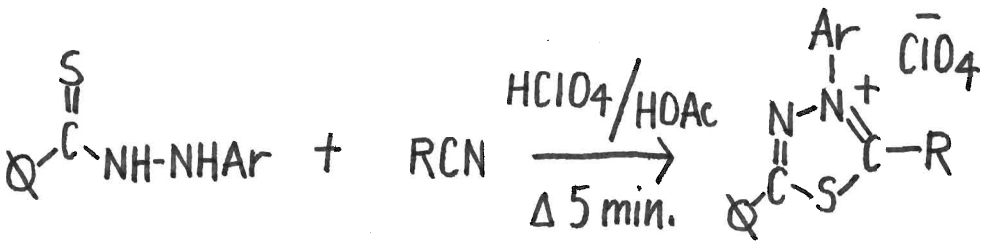
The stability of the thiadiazolium ion was thought to be responsible for these tranformations and similarly the salt (91) would be expected to lose ammonium perchlorate to give (93).

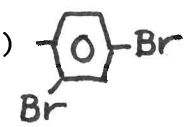


(91) (93)

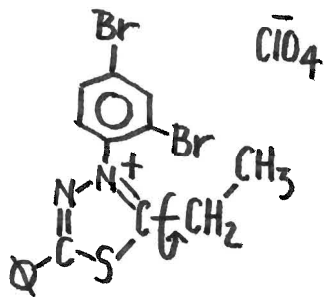
This was indeed found to occur and constitutes a convenient synthesis of these salts. The thiadiazolium salt could be removed from the reaction mixture by the addition of water, upon which it precipitated or oiled out. The results are summarized in Table 3.

TABLE 3



	Ar	R	yield	m.p. (°C)
(68)		CH_3	(82) 77%	173-174
(68)	"	CH_2CH_3	(83) 85%	196-198
(68)	"	ϕ	(84) 76%	266-268
(67)	ϕ	CH_3	(94) 77%	149-153
(67)	ϕ	ϕ	(95) 78%	215-218 (lit., 214-217°)[6]

Satisfactory elemental analyses were obtained for all of the salts prepared. The p.m.r. spectra of the 2-methyl salts (82) and (94) in deuterated acetonitrile showed signals for the methyl protons at 3.03 and 2.96 δ respectively. This is close to the average value of 3.1 (trifluoroacetic acid) observed by Boyd and Summers[7] for the 2-methyl protons of 1,3,4-oxadiazolium salts. The spectrum of the 2-ethyl salt (83) was somewhat unusual in that the methylene absorption was observed as a multiplet rather than the expected quartet. This was not further investigated, but may be due to restricted rotation about the methylene-carbon ring-carbon bond (96) brought about by the

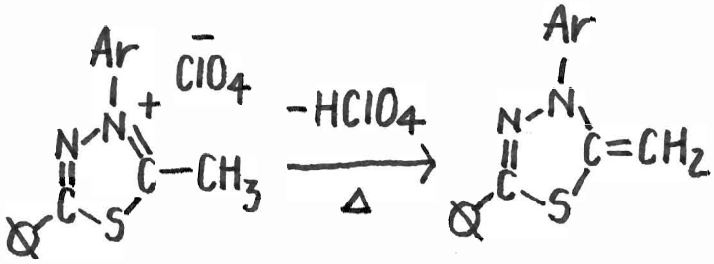


(96)

substituents on the 3 aryl group.

The $C=N^+$ stretch, 1620-1630 cm^{-1} was only clearly observed in the case of the 2-ethyl salt (83).

The mass spectra of the 2-methyl salts (82) and (94) showed peaks at the highest mass to charge ratio corresponding to the loss of perchloric acid, but the subsequent fragmentation was not very reproducible. The loss of perchloric acid to give the anhydrobase (97) is presumably a thermal process similar to the Hofmann degradation of

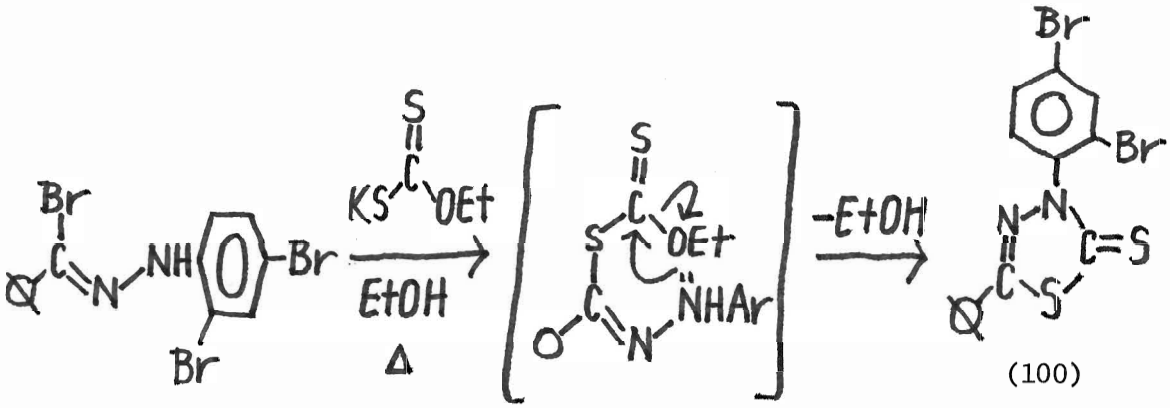


(97)

quaternary amines. A similar effect has been observed in the mass spectra of 1-alkyl-2-methylbenzothiazolium iodides[39] (98).

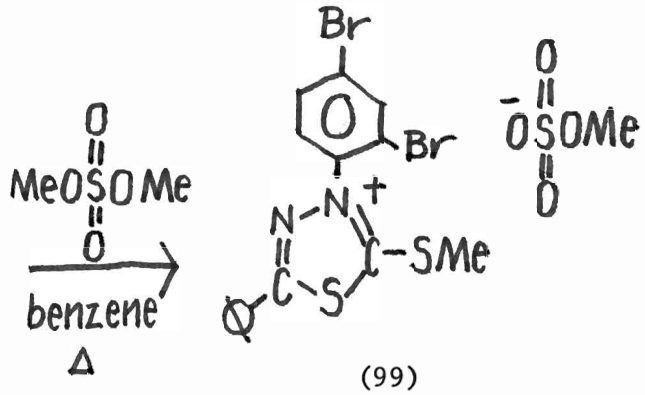
(98)

The other type of thiadiazolium salt prepared was the 2-methylthio derivative (99). This was made by methylating the 2-thione (100) which was obtained by the method of Fusco.[40]



(100)

(100)



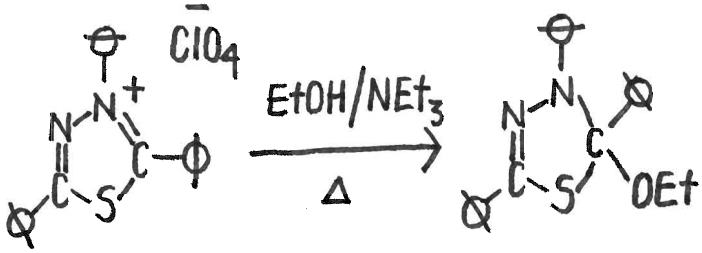
(99)

Several methylating agents, methyl iodide, methyl toluene-4-sulfonate, were tried, but after being refluxed with the thione for 12 h the presence of unreacted starting material was still observed (t.l.c.). Dimethylsulfate did however completely methylate the thione.

The methosulfate (99) was found to be quite hydroscopic, presumably losing methyl mercaptan on contact with water. This was shown to be true in experiments to be discussed subsequently. The mass spectrum of this compound was identical with that of the thione (100), indicating that it is thermally demethylated. A sample crystallized from acetic acid/benzene gave an unsatisfactory elemental analysis. It was, therefore, converted to the corresponding perchlorate which was found to be quite stable and gave an acceptable analysis.

3. REACTIONS OF 2-ALKYL AND 2-ARYL-1,3,4-THIADIAZOLIUM SALTS

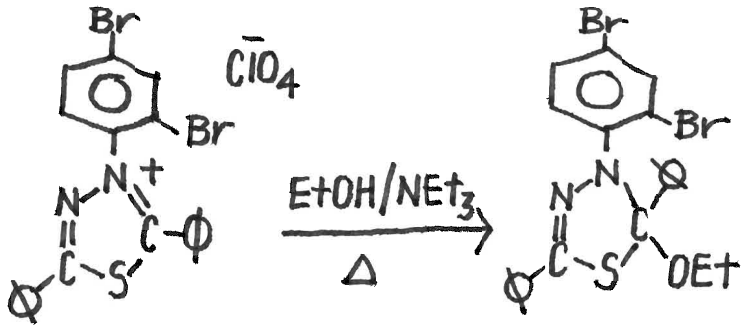
It has been shown[6,10] that 1,3,4-thiadiazolium salts react with nucleophiles at the 2-position. This was confirmed by refluxing



(95) (4)

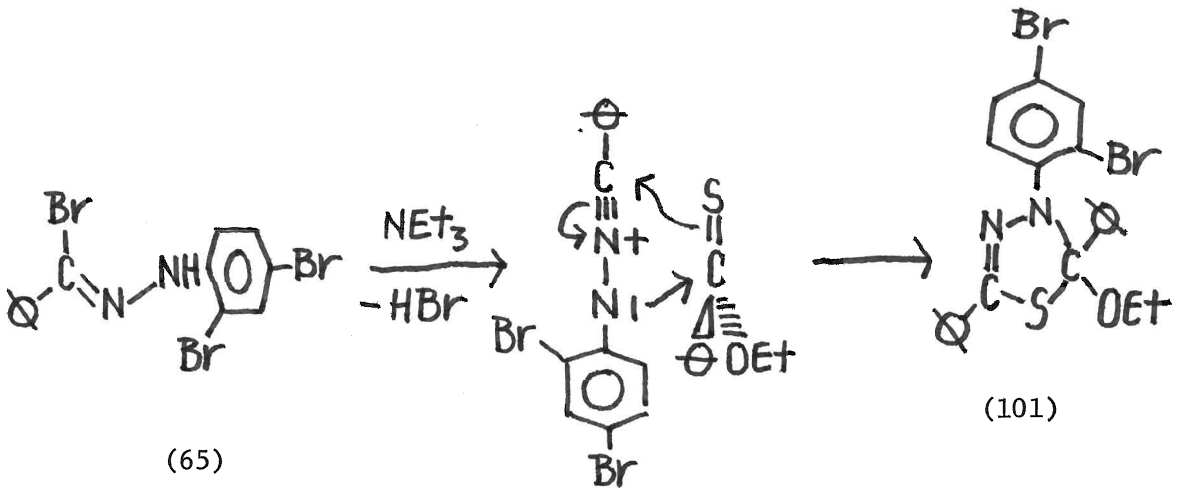
the triphenyl salt (95) in ethanol/triethylamine to obtain the known ethyl ether[3] (4).

Similar treatment of the salt (84) appeared to give the analogous



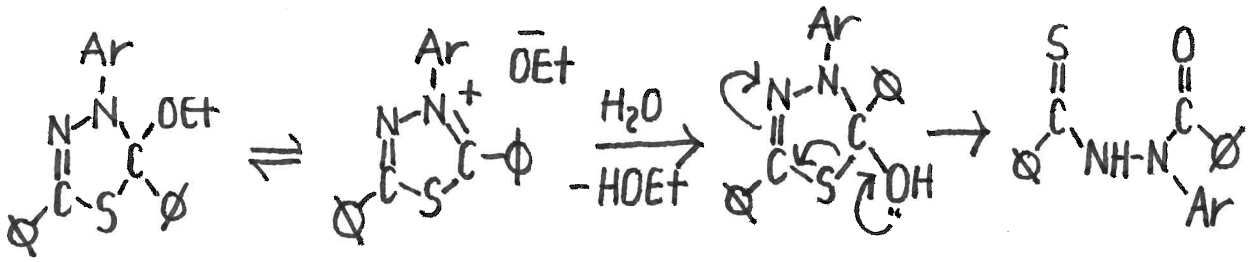
(84) (101)

ether (101) although the recrystallized compound melted over a broad range and gave a long streak rather than a single spot on a thin layer chromatogram. In order to be assured of its identity, it was prepared in a fashion analogous to that used by Huisgen and coworkers[3] to prepare (4). The 1,3-dipole (102), generated by the action of base on hydrazidic halide (65), was added across the thiocarbonyl group of



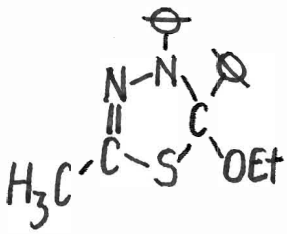
(65) (102) (101)

ethyl thiobenzoate to give the ether (101). This compound was found to have properties identical with that of the previously prepared compound. It was therefore thought that the decomposition of this compound at elevated temperature or on a t.l.c. plate was due to the stability of the thiadiazolium ion which could allow for the hydrolysis of the ether function in the absence of an acid catalyst. This was confirmed by refluxing the ethyl ether (101) in acetonitrile/water which resulted in the formation of the N'-benzoyl-benzothiohydrazide (71).



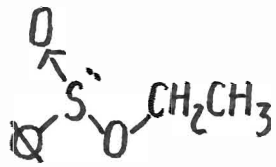
(101) (71)

The p.m.r. spectrum of this compound (101) was interesting in that the methylene absorption consisted of a multiplet rather than the expected quartet. This was also observed by Summers and Elguero[12] in the p.m.r. spectrum of the ethyl ether (103). They attributed the nonequivalence of the methylene protons to the asymmetric center present in the molecule but did not further investigate this situation. It was therefore decided to examine it more closely.



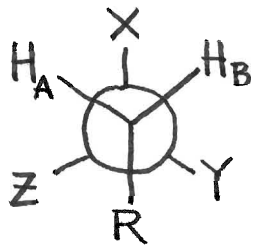
(103)

This type of nonequivalence was first correctly interpreted by Waugh and Cotton[41] who observed an ABX_3 splitting pattern for the ethyl portion of the sulfinate ester (104). They considered the situation

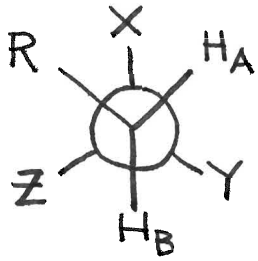


(104)

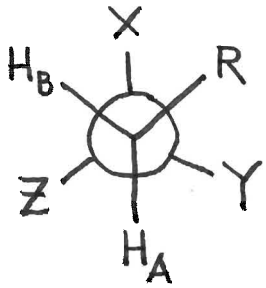
to be essentially the same as that described by Pople[42] for simple substituted ethanes. Considering the molecule $RH_AH_BC\text{-}CXYZ$ in a staggered configuration, there are three possible rotational isomers (105), (106), and (107). If the rotation is slow and unhindered, the spectrum would



(105)



(106)

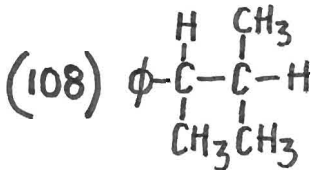


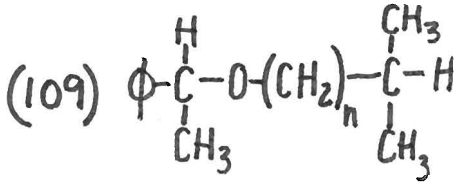
(107)

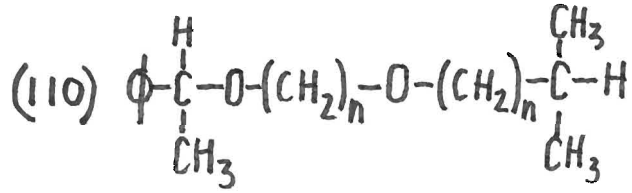
consist of three AB patterns. However, even if the rotation is rapid and unhindered, the averaged environment of H_A will always differ from that of H_B and an AB pattern will be observed. That is, since there is not a symmetry plane along the axis of rotation, the environments of H_A and H_B in one rotational isomer cannot be found reversed in another and they therefore cannot be averaged into an A_2 system.

That this analysis is applicable to a system where the asymmetric center is several bonds removed was shown by Roberts and coworkers[43]. The shift difference between the methyl protons of the isopropyl group were examined in compounds (108), (109) and (110). It was found that the

$\nu(CH_3)_A - \nu(CH_3)_B$ (c.p.s., benzene)

(108)  8.0

(109)  $n=0$ 0.8; $n=1$ 0.5; $n=2$ 1.8

(110)  $n=0$ 0.8; $n=1$ 0.0

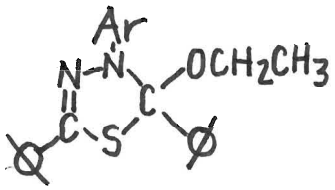
shift difference decreased, but remained observable, until there were five bonds separating the asymmetric center from the methyl groups. At this point, which with respect to the substituents on the asymmetric carbon is in accord with Newman's "rule of six", the shift difference was found to increase. After this point it again decreased and finally vanished.

The methylene portion of the ethyl ether (101) is shown in Figure 2. Using the splitting diagram, the shifts of the AB quartet were found, the J_{AX} or J_{BX} coupling constant being approximately 7 Hz. From the shifts of the AB quartet, ν_A and ν_B were calculated.[44] Using these values, along with the observed spectrum an iterative computer program[45] gave a simulated spectrum which best fit the data given. Unfortunately, the computer size did not allow one to obtain the shift values for the individual peaks in the iterated spectrum but, as can be seen from Figure 3, with a line broadening of 1.0 Hz, a fairly good fit was obtained.

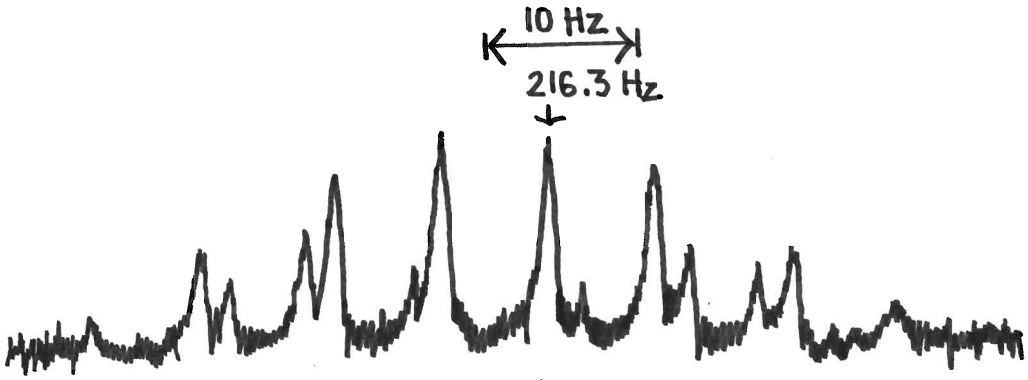
Saturating the methyl protons caused the methylene multiplet to collapse to the expected AB quartet (Figure 4a) and running the spectrum at 50°C (Figure 4b) did not alter the spectrum thereby ruling out restricted rotation.

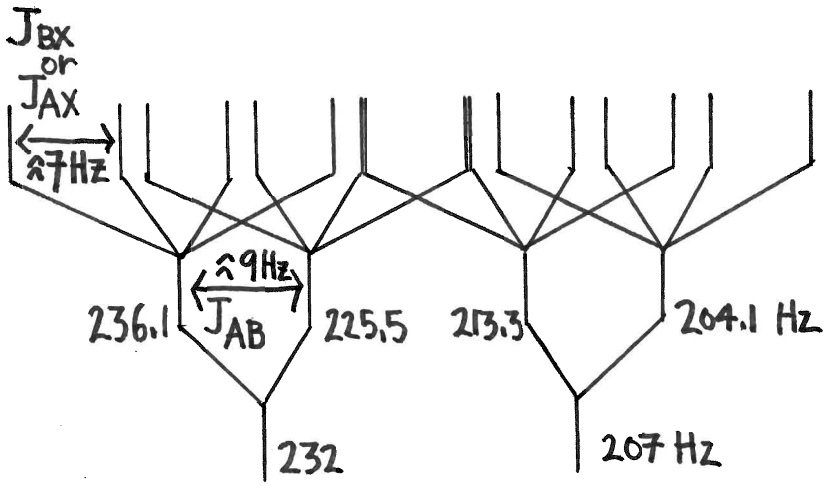
FIGURE 2

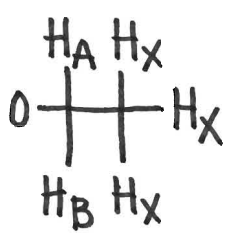
Methylene portion of the p.m.r. spectrum of



(101)







$J_{AX} \approx J_{BX} \approx 7$ Hz

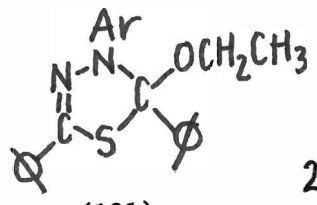
$J_{AB} \approx 9$ Hz

$\nu_A = 232$ Hz

$\nu_B = 207$ Hz

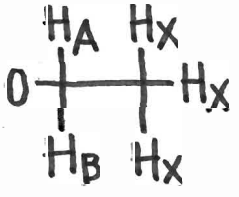
FIGURE 3

Methylene portion of



(101)

ITERATED VALUES FOR:



$J_{AX} = 6.90$ Hz

$J_{BX} = 7.18$ Hz

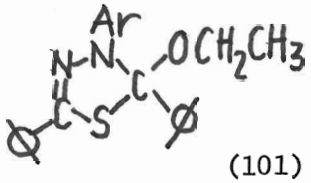
$J_{AB} = 9.01$ Hz

$\nu_A = 230.3$ Hz

$\nu_B = 209.0$ Hz

FIGURE 4a

The effect of decoupling the methyl protons of



(101)

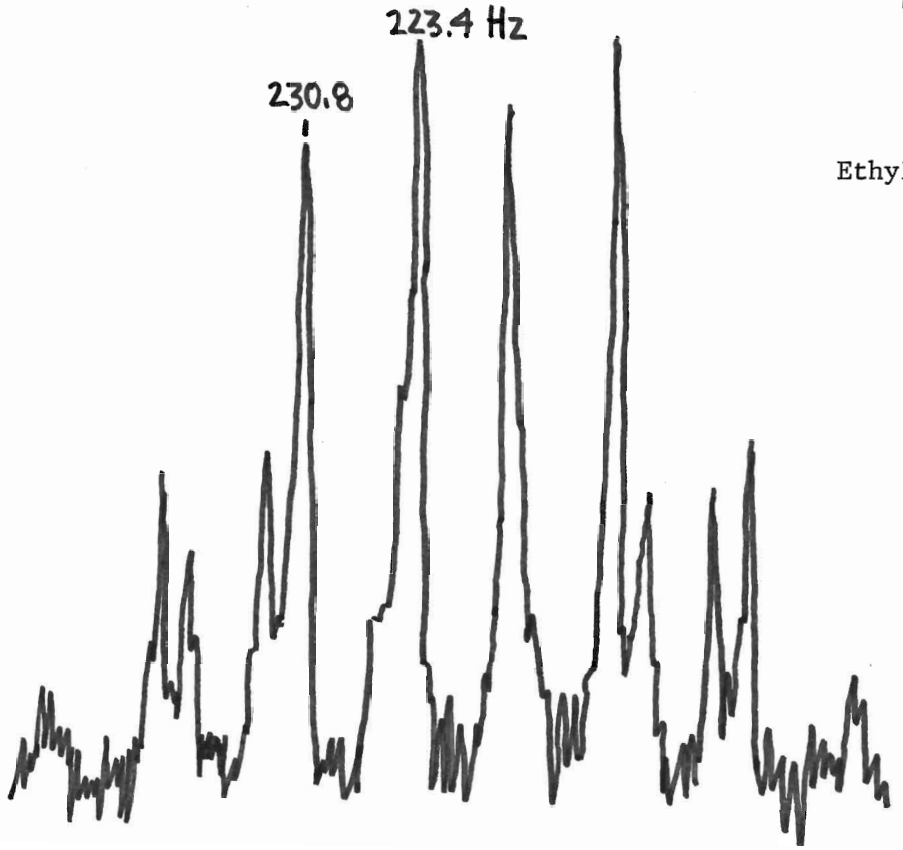
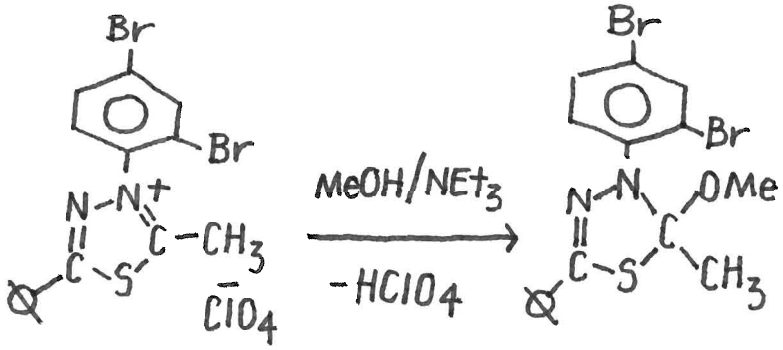


FIGURE 4b

Ethyl portion of (101) at 50°C

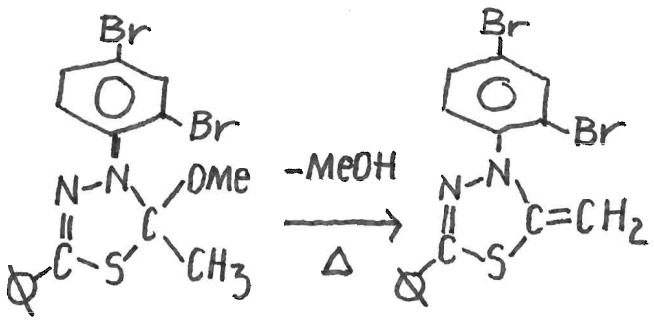
The 2-methyl salt (82) was treated with methanol/triethylamine in the hope that the methyl ether (111) would be obtained. This yielded



(82) (111)

an unstable crystalline solid which tended to decompose on attempted crystallization and also upon standing. It was found to melt over a broad range and appeared to bubble while doing so. The mass spectrum did not show a molecular ion; rather the peak with greatest mass to charge ratio corresponded to (111) having lost methanol. The subsequent fragmentation, particularly the distinctive loss of Br, seemed to originate from this peak. However the p.m.r. spectrum and elemental analysis did correspond to the ether (111).

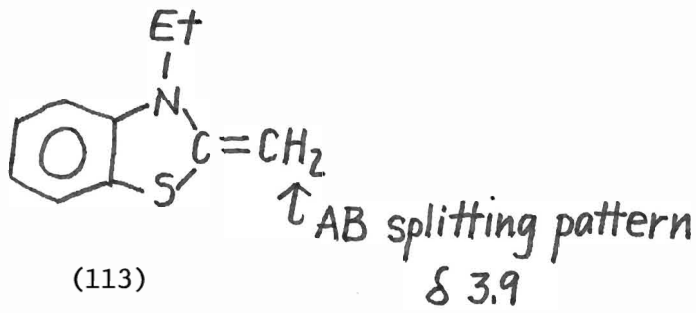
These observations suggested that the methyl ether was formed but that it readily lost methanol to give the anhydrobase (112). It was therefore decided to prepare the anhydrobase and compare it with the decomposition products of the methyl ether.



(111) (112)

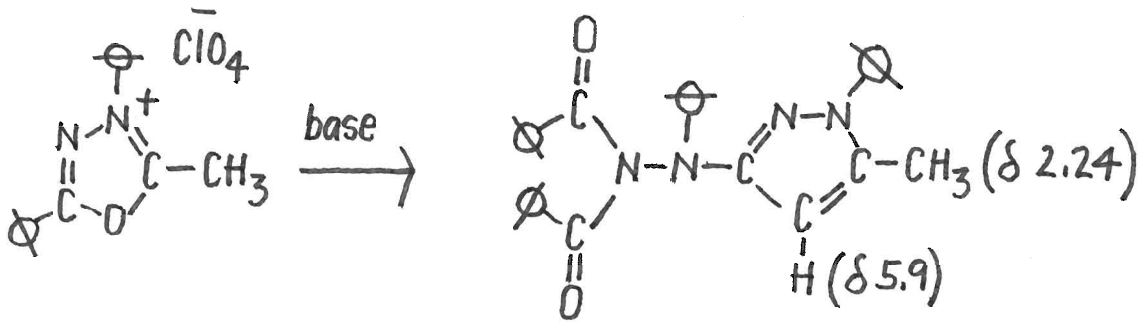
Treatment of the 2-methylthiadiazolium salt (82) in dry acetonitrile with triethylamine gave an unstable yellow solid. The elemental analysis was found to be in agreement with a monomeric or dimeric anhydrobase. The mass spectrum seemed to vary giving high mass clusters which were less than that expected for the dimer and greater than that for the monomer. The differences did not seem to be accountable by simple fragmentation or recombination. However, when a low probe temperature was used, a two bromine cluster at m/e 412/410/408, corresponding to the anhydrobase, was observed as the highest peak.

Excluding the aromatic region, the p.m.r. spectrum of this compound showed singlets at 1.8 and 4.3 δ corresponding to 3 and 1 protons respectively. This would exclude the monomer (112) since one would expect a chemical shift and splitting pattern similar to that observed by Owen[46] for the anhydrobase (113).

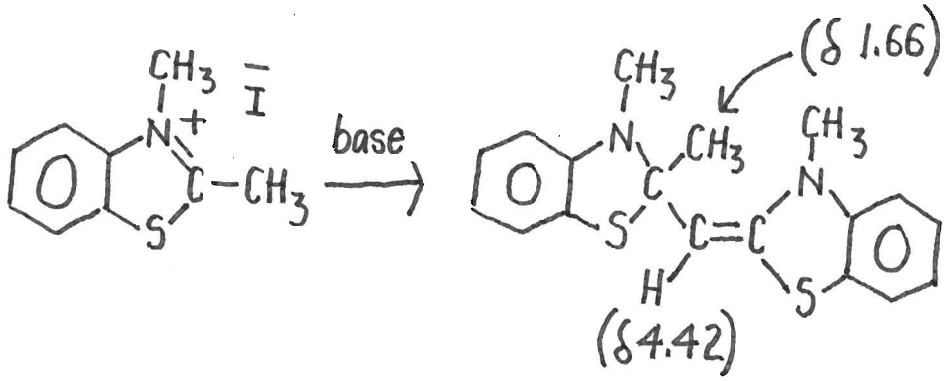


(113)

There were then two possible dimeric structures for this compound, one corresponding to Boyd's dimer[14] (40) and the other corresponding to (114)[47]. On the basis of chemical shifts, the dimer (115)

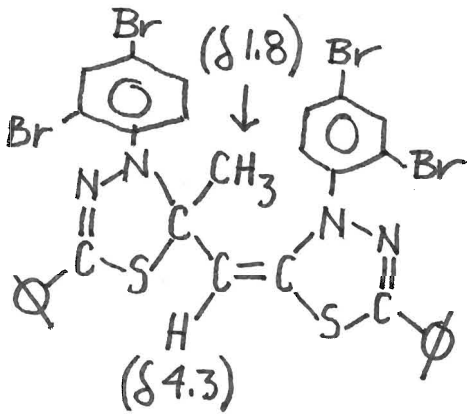


(40)



(114)

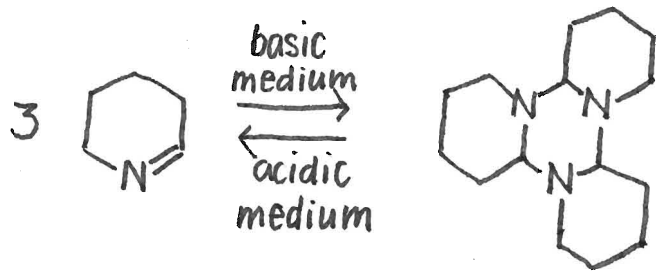
analogous to (114) would offer the best fit, since if the methyl and olefinic protons were part of a pyrazole ring as in (40), one would



(115)

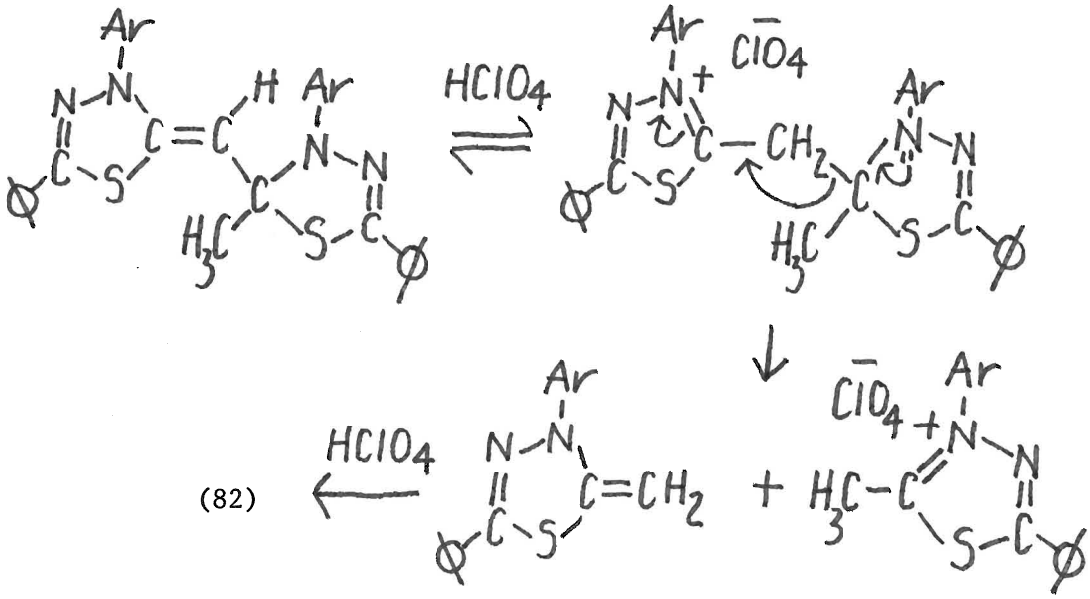
expect them to be shifted to lower field.

Since enamine dimers or trimers (116) generally revert to monomers under acidic conditions;[20] the dimer was refluxed in acetic acid/perchloric acid.



(116)

This was found to give the 2-methyl salt (82) which further supports the structure (115) since a "dimer" analogous to the pyrazole (40) would



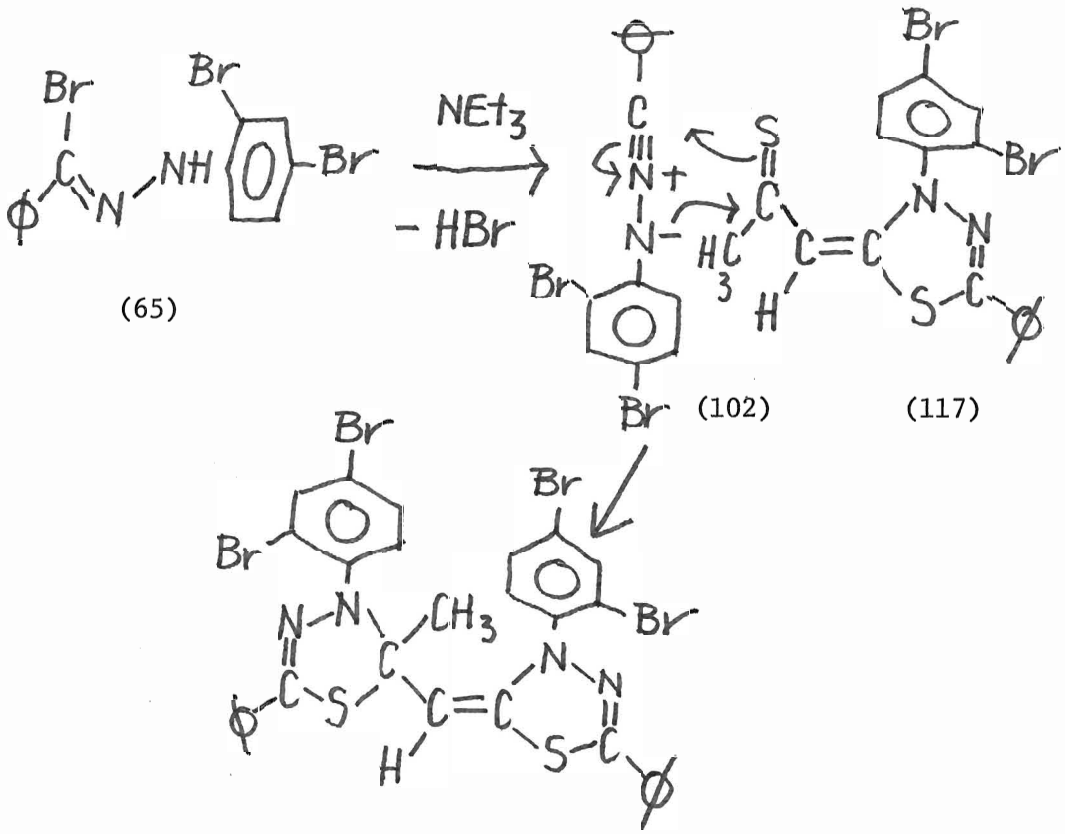
(82)

(82)

not be expected to revert to the 2-methyl salt (82).

As a further check on the structure, the dimeric compound (115) was prepared by an alternate route. The thioacetonylidene compound (117), whose structure and synthesis will be discussed subsequently,

was treated with the hydrazidic halide (65) in the presence of triethylamine. The 1,3-dipole (102) generated under these conditions adds across the thiocarbonyl group as was observed in preparation of the ethyl ether (101).



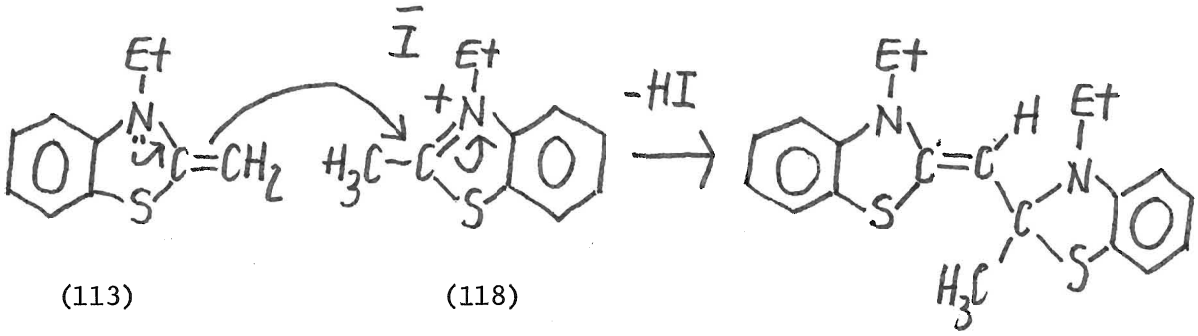
(65) (102) (117)

(115)

The melting point of this compound was somewhat lower than that of the authentic sample but unfortunately, like the authentic sample, it could not be recrystallized without causing it to decompose. The p.m.r. spectrum was identical with that of the dimer (115) except for a small peak at 2.7 δ, presumably corresponding to the methyl protons

of (117). The identity of this product and the presence of traces of unreacted (117) were further confirmed by t.l.c.

That a dimer rather than a monomer was formed in the reaction of the 2-methyl salt (82) with base is supported by the work of Owen[46] who isolated the monomeric form of the benzothiadiazole anhydrobase (113). In this instance, the mechanism of dimer formation was thought to involve the reaction of the anhydrobase with the conjugate acid (118) present in the same medium. Owen used a two phase system where



(113) (118)

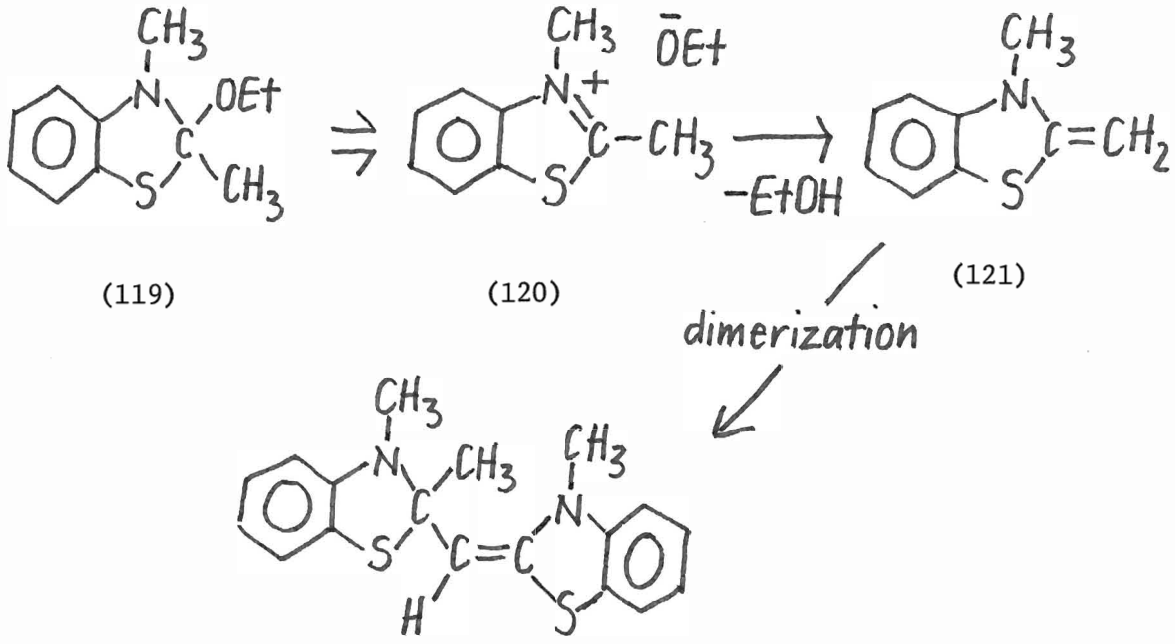
the anhydrobase went into an inert non polar solvent as it was formed. The conjugate acid (118) was not soluble in this medium and therefore dimerization did not occur. These reactions did however have to be conducted in an inert atmosphere since it was found that the anhydrobase dimerized on exposure to air.

As previously mentioned, the dimer was found to be unstable, decomposing to a variety of red-coloured products (t.l.c.). These products were not investigated but it should be noted that the pyrazole (40) was obtained from the 2-methyl salt (39) on treatment with base for 12 h, whereas the dimer (115) resulted after only brief treatment with base. It may be that (115) would, after prolonged exposure to base, undergo a similar type of rearrangement.

Considering the decomposition products of the methyl ether (111), a sample in a p.m.r. tube was heated at approximately 70°C for 5 min, allowed to cool to room temperature, and its spectrum was taken. This process was repeated again and the results are shown in Figure 5.

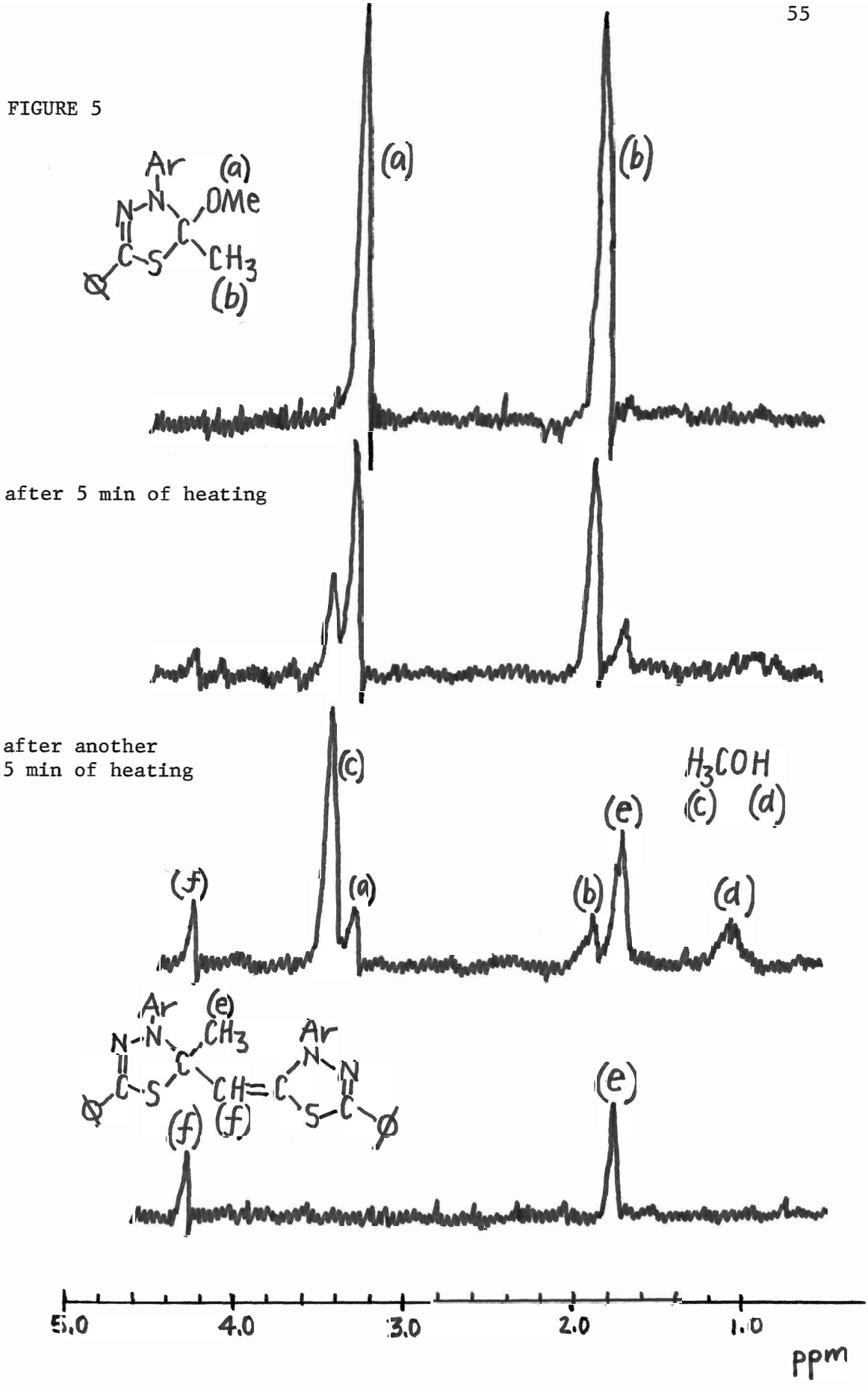
After the heating process had been repeated, the two methyl signals of the methyl ether had considerably shrunk in size and the peaks at 1.8 and 4.3 δ, corresponding to the dimer, became quite distinct. The signals at 3.4 and 1.1 δ were attributed to methanol, the accepted values being 3.5 and 1.7 δ[48] although the shift of the hydroxy proton is quite concentration dependent.

It therefore appears that the methyl ether (111) loses methanol on heating to give the anhydrobase which then dimerizes. A similar sort of behaviour was observed for the ethyl ether[49] (119) using the u.v. technique. The postulated mechanism involved the ionization of



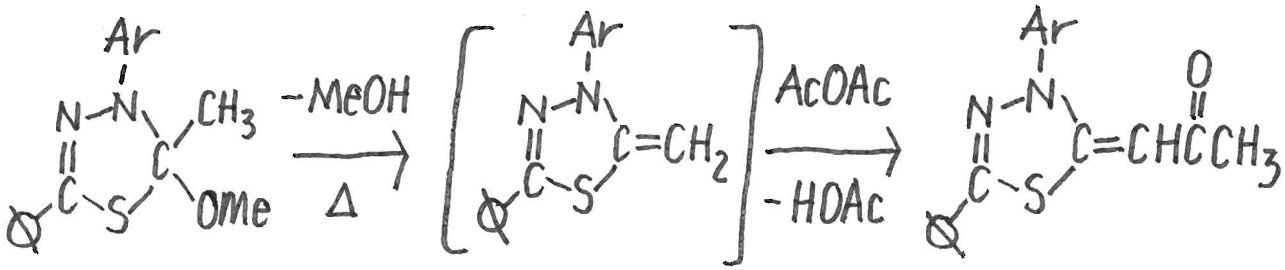
(119) (120) (121)

FIGURE 5


Ar
(a)
N-N
OMe
C
C-S
CH3
Ø
(b)
(a)
(b)
after 5 min of heating
after another
5 min of heating
(c)
H3COH
(c) (d)
(e)
(f)
(a)
(b)
(d)
Ar
(e)
N-N
CH3
C
C-S
CH=C
Ar
N
N
C-S
Ø
(f)
(f)
(e)
5.0
4.0
3.0
2.0
1.0
ppm

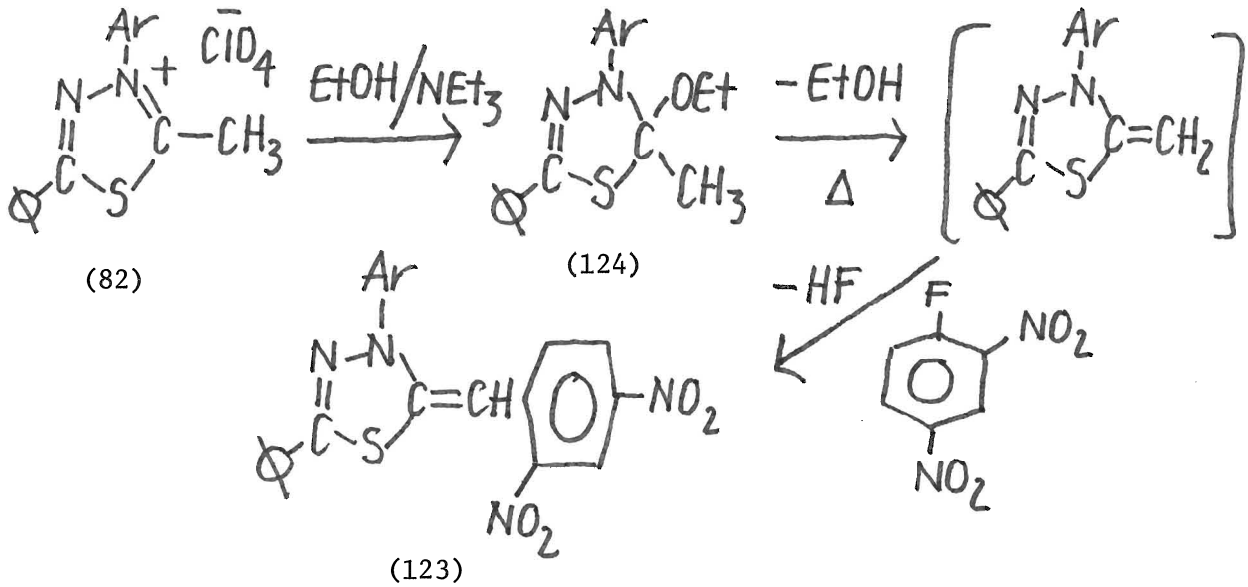
the ethyl ether (119) which then underwent the loss of ethanol to give the anhydrobase (121). This could then dimerize by reaction with the ionized species (120) or by exposure to air, since an inert atmosphere was not used.

The existence of the anhydrobase as a decomposition product of the methyl ether (111) was further verified by trapping it with acetic anhydride. When the methyl ether was refluxed in acetic anhydride, the acetonylidene compound (126) whose identity will be discussed in the next section, was obtained.



(111) (126)

Reaction of the 2-methyl salt (82) with 2,4-dinitrofluorobenzene in ethanol/triethylamine gave the 2,4-dinitrobenzylidene derivative (123). This reaction presumably involves the initial formation of the

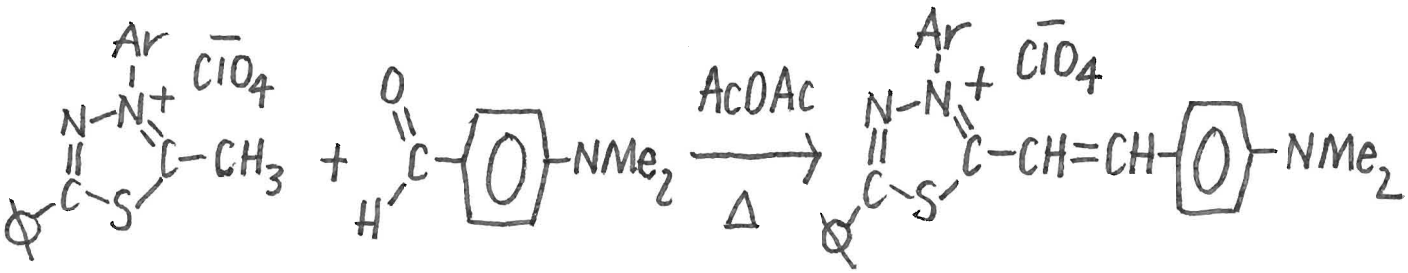


(82) (124) (123)

ethyl ether (124) which thermally loses ethanol to give anhydrobase which then reacts with the dinitrofluorobenzene. It was noted that addition of triethylamine to a suspension of the salt in ethanol containing the 2,4-dinitrofluorobenzene resulted in a yellow suspension. The distinctive red colour of the benzylidene derivative (123) was not observed until the solution was heated.

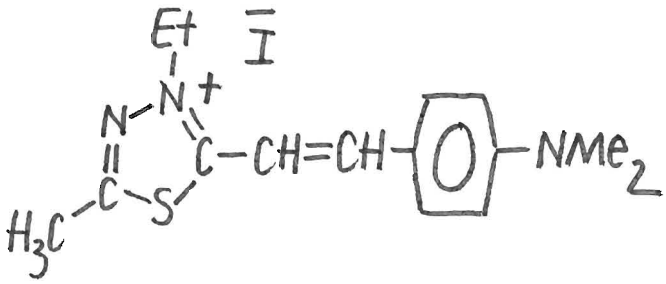
4-Fluoronitrobenzene did not react with the 2-methyl salt (81) under similar conditions to give the previously obtained 4-nitrobenzylidene derivative (80). Presumably the 4-fluoro group is not sufficiently activated for nucleophilic displacement.

Reaction of the 2-methyl salt (82) in acetic anhydride with p-dimethylaminobenzaldehyde gave the styryl dye (124). This would be an example of a mixed aldol condensation referred to in the introduction.



(82) (124)

The styryl dye crystallized as dark green crystals but gave a purple solution when dissolved in ethanol (λ_{max} 555 nm). A similar styryl dye (125), prepared by Brooker and coworkers[17], had an absorption maximum at 498 nm. The bathochromic shift is probably due to the

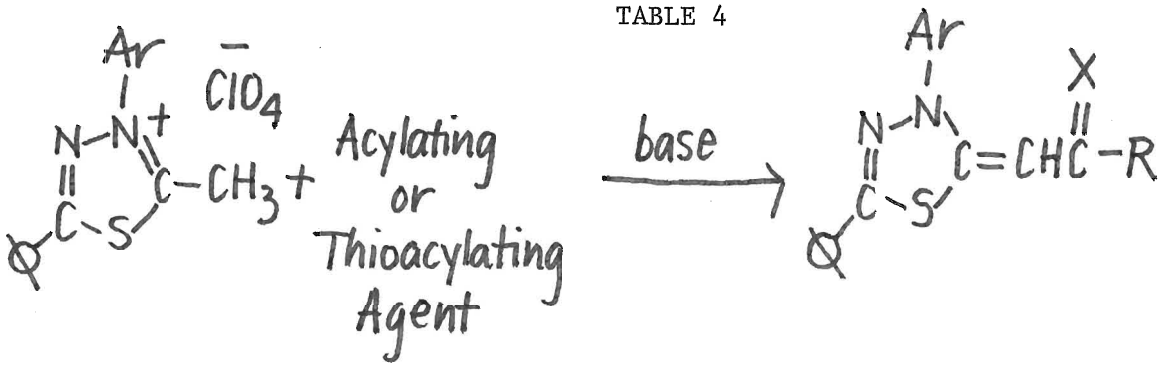


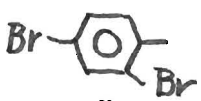
(125)

presence of the 3 and 5 aryl substituents since extra-chromophoric conjugation can augment the "basicity" of one of the dye nuclei[50] and bring about a deepening in colour.

The last series of reactions performed with the 2-methyl salts involved the acylation and thioacylation of their conjugate bases. The results of these reactions are listed in Table 4. The structural

TABLE 4



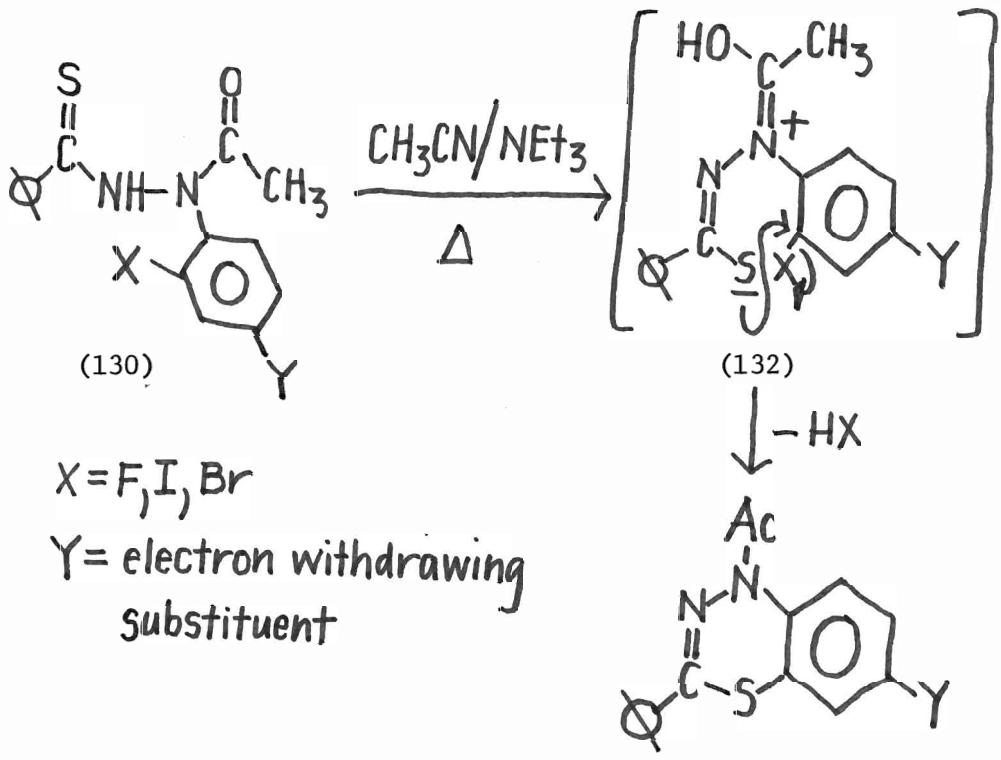
	Ar				yield	X	R
(82)		AcOAc	NaOAc	(126)	76%	O	CH_3
(82)	"	$(CH_3CH_2C)_2O$	NaOH	(127)	55%	O	CH_2CH_3
(82)	"	$\phi CSCH_2COH$	NH_3/EtOH	(128)	68%	S	ϕ
(94)	ϕ	CH_3CCl		(129)	50%	O	CH_3

aspects of these compounds will be discussed in the next section.

2. ACYL DERIVATIVES OF THE ANHYDROBASE

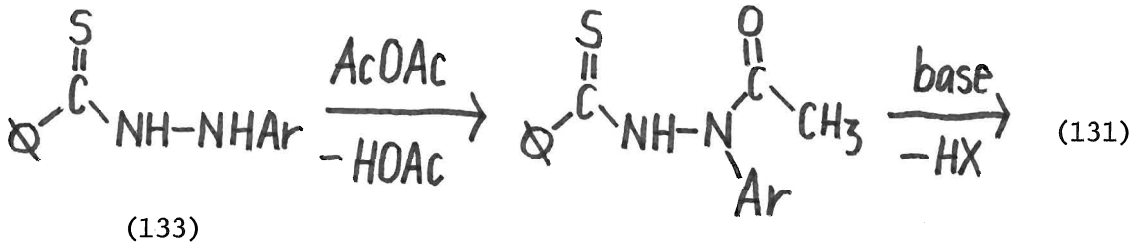
Since several acyl and thioacyl derivatives of the anhydrobase have been described in the preceding section, the nature of the interest in these compounds will now be discussed.

Acetylated thiohydrazides[24] (130) have been shown to undergo facile ring closure in refluxing acetonitrile/triethylamine to give benzothiadiazines (131). The reaction intermediate (132) was thought



to contain a quaternized nitrogen which activated the 2-halogen toward nucleophilic attack by sulphur.

In attempting to expand the experimental conditions for this reaction, Callaghan[24] thought that acetylating the thiohydrazide (133) in the presence of excess base would result in benzothiadiazine formation.



(133) (131)

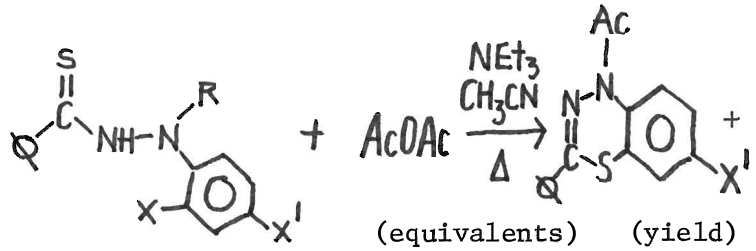
His results along with those of Vukov[25], who subsequently examined the reaction, are summarized in Table 5.

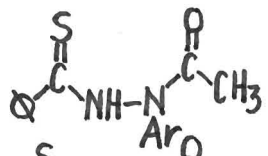
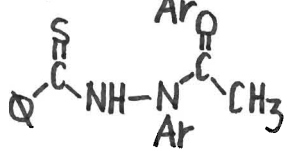
As can be seen from this table, when low concentrations of acetic anhydride were used, the benzothiadiazine along with the acetylated thiohydrazide were formed. However, when the concentration was increased, the yield of the benzothiadiazine became negligible and a new product was formed. The acetylated thiohydrazide was shown to react similarly and it was found that that basic conditions were not necessary for the formation of this new product.

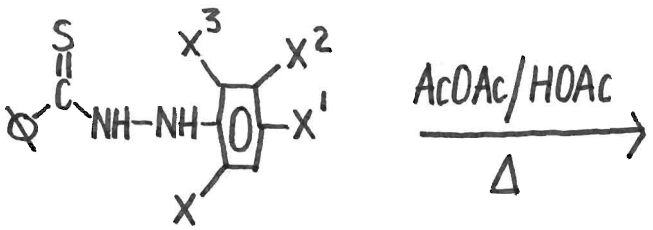
From their spectroscopic data, summarized below, and their

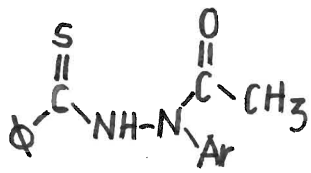
p.m.r. (δ)	singlet, 2.1-2.2 (3H)	suggesting $-\overset{\overset{O}{\|}}{C}CH_3$
	singlet, 5.5-5.6 (1H)	$=C\begin{matrix}/\\ \backslash H\end{matrix}$
	multiplet, 7-8	aromatic protons
i.r. (cm^{-1})	≃ 1600(νC=O)	$-N-\overset{\overset{O}{\|}}{C}CH_3$
m.s.	M^+-CH_2CO, $CH_3\overset{\overset{O}{\|}}{C}\cdot$	$-\overset{\overset{O}{\|}}{C}CH_3$

TABLE 5



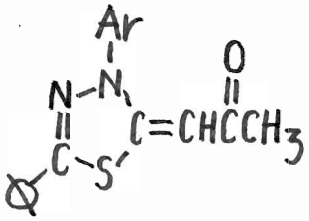
	(equivalents)	(yield)		
R = H, X = F, X' = I	1.5	38%		(t.l.c.)
R = H, X = X' = Br	2	8%		(36%)
R = H, X = X' = I	excess	5%	$C_{17}H_{12}I_2N_2OS$	(45%)
R = H, X = F, X' = I	excess	3%	$C_{17}H_{12}FIN_2OS$	(43%)
R = H, X = X' = F	excess	traces	$C_{17}H_{12}F_2N_2OS$	(67%)
R = Ac, X = X' = Br	excess	traces	$C_{17}H_{12}Br_2N_2OS$	(94%)
R = Ac, X = X' = F	excess	traces	$C_{17}H_{12}F_2N_2OS$	(69%)



		product (yield)	
$X = X^3 = Br$, $X^1 = X^2 = H$	(Δ20 min.)		
$X = X^2 = Br$, $X^1 = X^3 = H$		$C_{17}H_{12}Br_2N_2OS$	(84%)
$X = X^1 = X^3 = Br$, $X^2 = H$		$C_{17}H_{11}Br_3N_2OS$	(100%)
$X = X^1 = Br$, $X^2 = X^3 = H$		$C_{17}H_{12}Br_2N_2OS$	(94%)

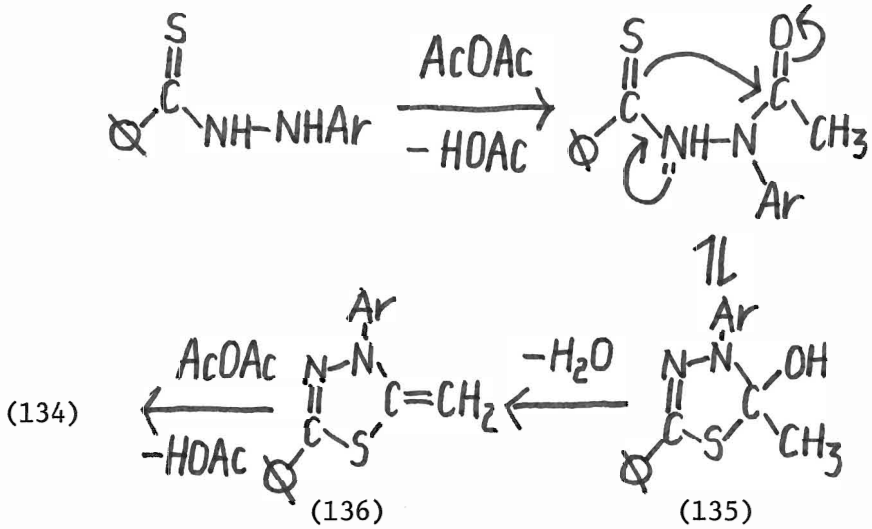
elemental analyses, it was concluded that the thiohydrazide was twice acetylated and once dehydrated. It was also found that they resisted acid hydrolysis indicating that the acetyl group was not attached to a secondary nitrogen.

From this information, the most reasonable structure seemed to be a thiadiazoline (134). This was thought to arise through the acetylation



(134)

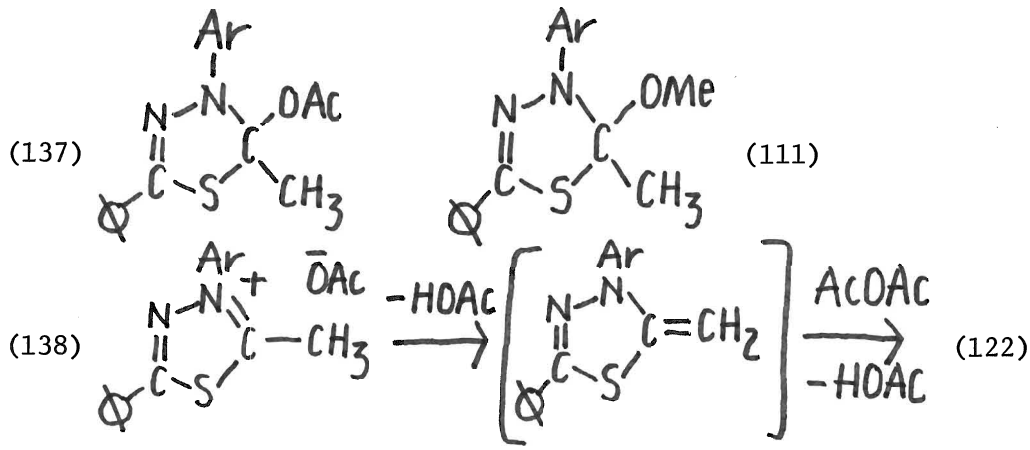
of the thiohydrazide which could then cyclize through a five-membered transition state to give the thiadiazoline (135). Loss of water would



give the anhydrobase (136) which could then be acetylated to give the product (134).

The validity of most aspects of this mechanism has been established in the preceding section. Acylbenzothiohydrazides have been shown to cyclize in acetic anhydride using perchloric acid to give thiadiazolium salts. These salts have been shown to give rise to anhydrobases on treatment with base and as a result could be acylated.

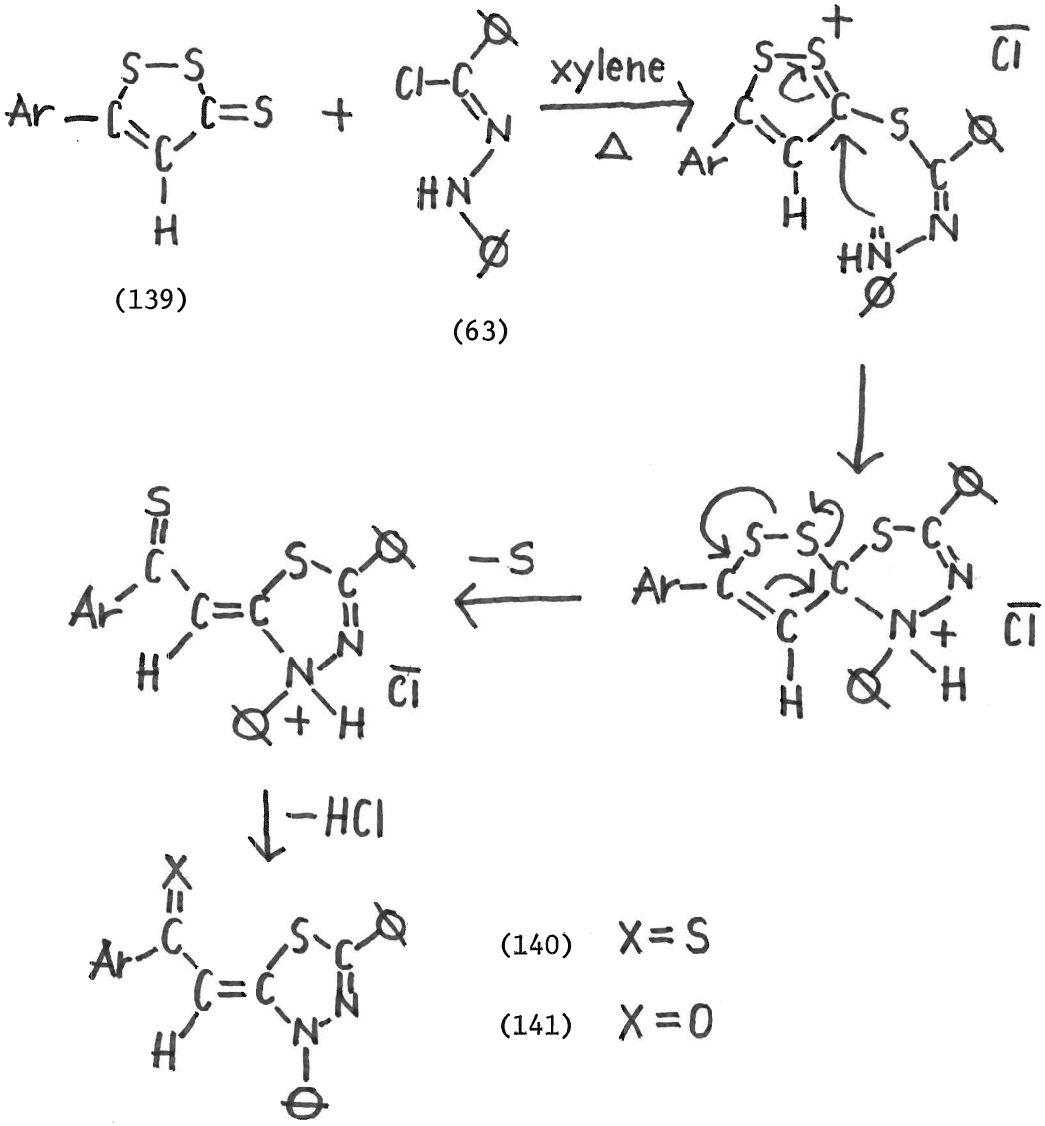
The point of difference is that the initial cyclization is brought about by acetic anhydride and elevated temperatures. One would therefore expect the structure of the cyclized intermediate (135) to be (137).



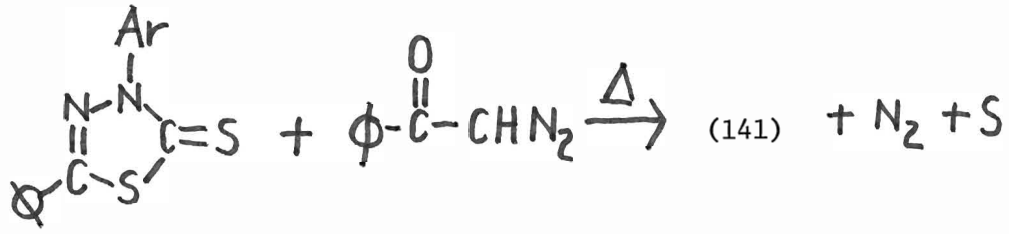
This would be analogous to (111) which has been shown to lose methanol on being heated to give the anhydrobase. The acetate would be expected to undergo ionization much more readily to give the acetate salt (138), since it is a better leaving group than the methoxide ion. That this species can give rise to the anhydrobase was shown when the 2-methyl-thiadiazolium perchlorate was refluxed with an equivalent of sodium acetate to give the thiadiazoline (122).

There are only two literature references to a thiadiazoline such as (134). The first is by French workers[51] studying the chemistry of 5-aryl-1,2-dithiol-3-thiones (139). These thiones were found to react

with the hydrazonyl halide (63) to give the thioacetophenone (140). The following mechanism was proposed:

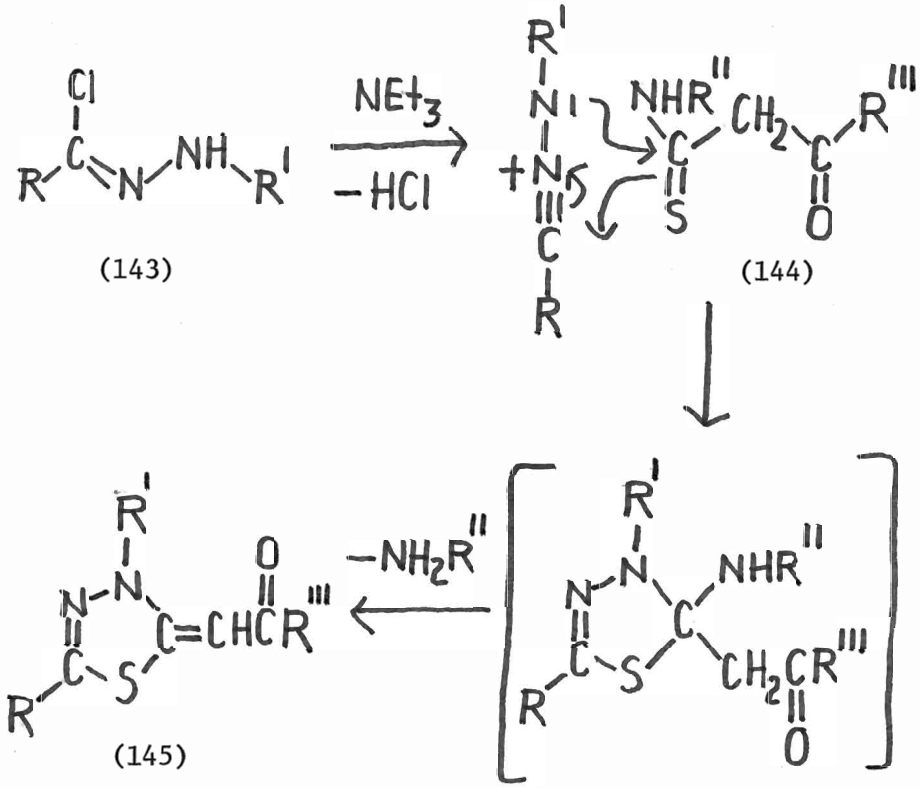


Oxidation of (140) with mercuric acetate gave the corresponding acetophenone (141) which could be reconverted to the sulphur analogue (140) by reaction with phosphorus pentasulfide. The structure of (141) was confirmed by independent synthesis from diazoacetophenone and the 2-thione (142).



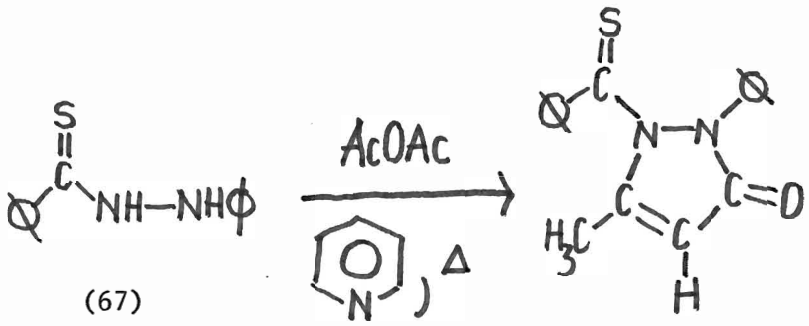
(142)

The other reference is by Italian workers[52] who found the 1,3-dipole, generated by the action of base on the hydrazonyl chloride (143), to add across the thiocarbonyl group of the anilides of β-keto thioacids (144). The intermediate thiadiazoline was thought to lose the amine moiety to give (145).



(143) (144) (145)

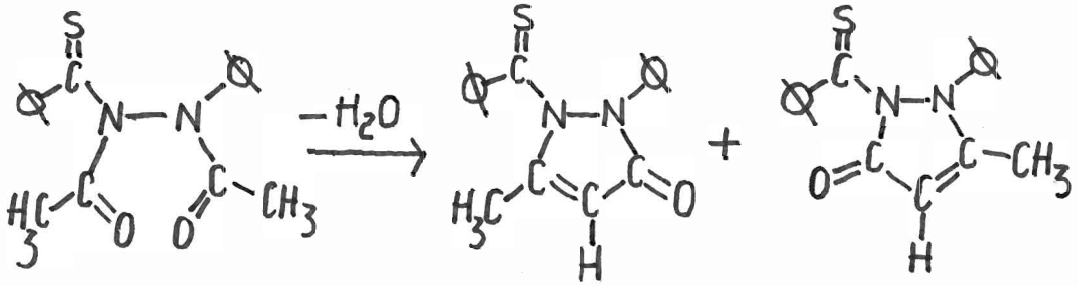
Recently, Barton and coworkers[26] reported the reaction of the thiohydrazide (67) with acetic anhydride in the presence of pyridine. Although the product had analogous spectral properties to those given by Callaghan and by Vukov, they proposed a pyrazolone structure (146).



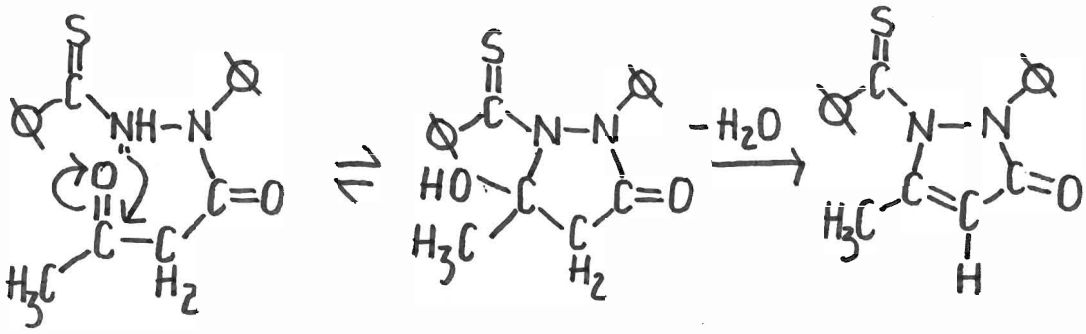
(67) (146)

This would be a new type of pyrazolone, there not being any literature mention of such an N-acyl or thioacylpyrazolone, but they did not attempt an independent synthesis or further investigation of the reaction.

It is difficult to propose a mechanism which would give rise to Barton's pyrazolone. The two most reasonable precursors would be the diacetylated thiohydrazide (147) and the acetoacetylated thiohydrazide (148). The diacetyl derivative (147) could give rise to two isomeric pyrazolones although only one was observed. The acetoacetylated derivative (148), presumably arising through C-acetylation of the

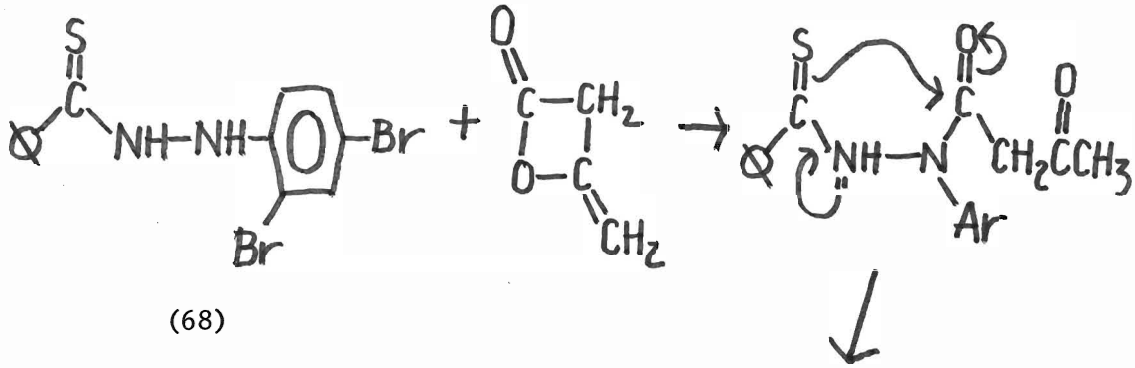


(147)

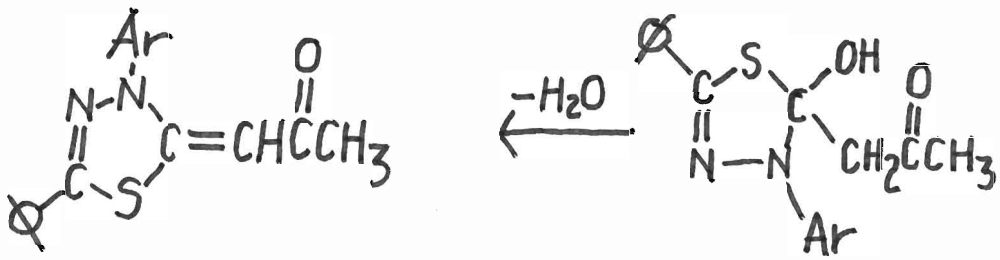


(148)

acetylated thiohydrazide, could undergo ring closure through attack by nitrogen and lose water to give the pyrazolone. An acetoacetylated



(68)



(126)

intermediate similar to (148) was also considered by Elliott[54] who treated the thiohydrazide (68) with diketene and obtained a compound identical with that prepared earlier by Callaghan. In this instance, it is more reasonable to propose a thiadiazoline structure (126) since

the compound was shown to be resistant to acid hydrolysis and the thiobenzoylpyrazolone would be expected to hydrolyze readily.

Since Callaghan and Vukov had prepared a variety of these compounds differing in the nature of the halogens present on the 3-aryl substituent, it was decided to examine the scope of the reaction by using the N'-2,4-dibromophenyl- and phenylbenzothiohydrazides (68) and (67), and varying the nature of the acid anhydride used. Using the N'-acetyl-N'-phenylbenzothiohydrazide (72) with benzoic anhydride and (67) with acetic anhydride would allow for the preparation of the thiadiazoline (141) prepared by the French workers and also the Barton compound. Performing similar reactions with the 2,4-dibromophenylbenzothiohydrazide would keep the reactions within the series started by Callaghan and Vukov. The results are listed in Table 6.

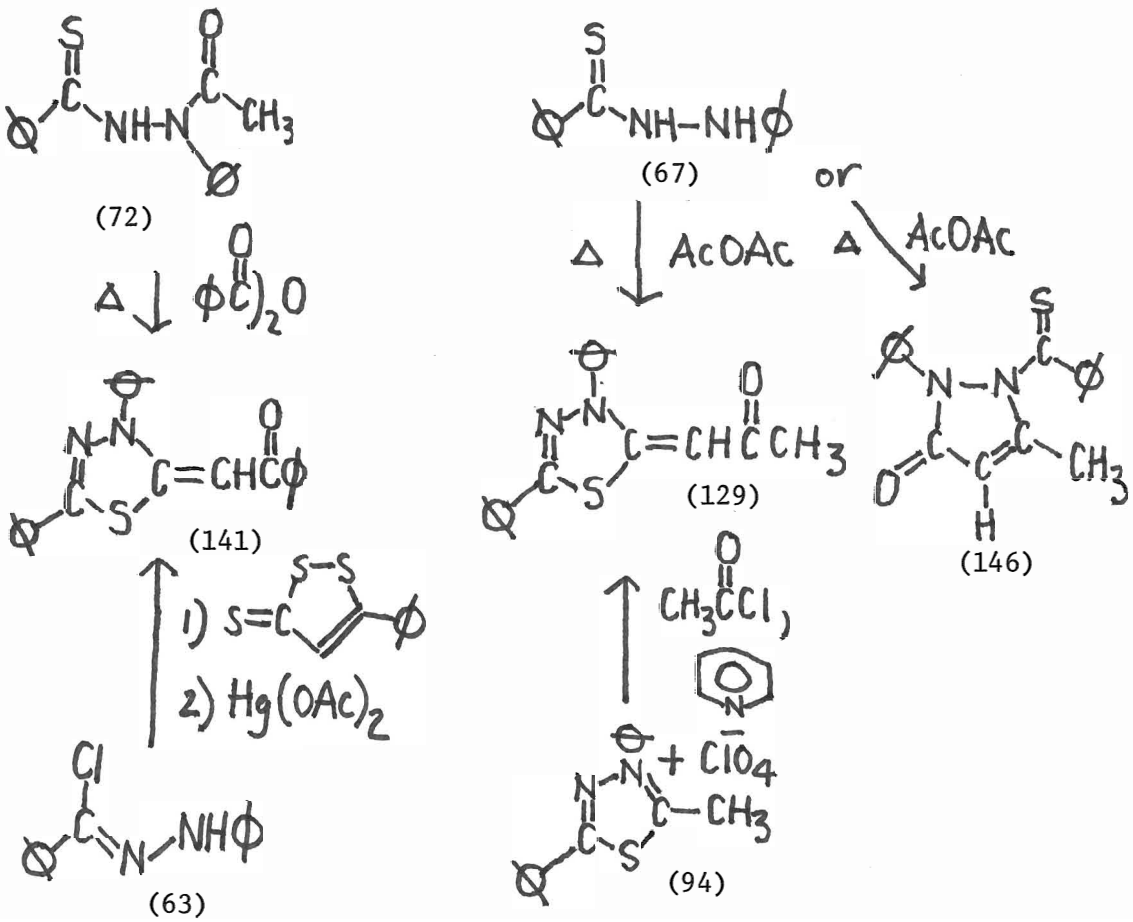
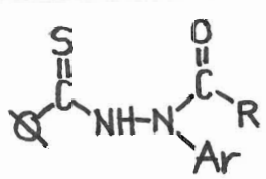
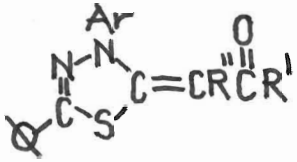
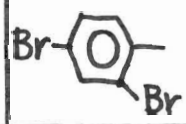
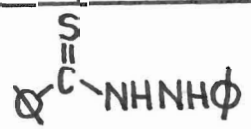
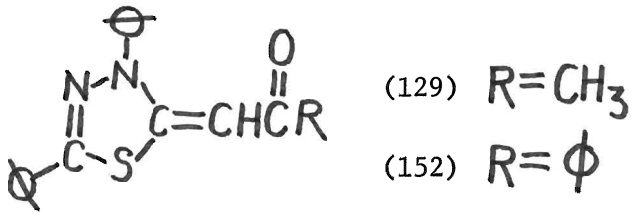


TABLE 6

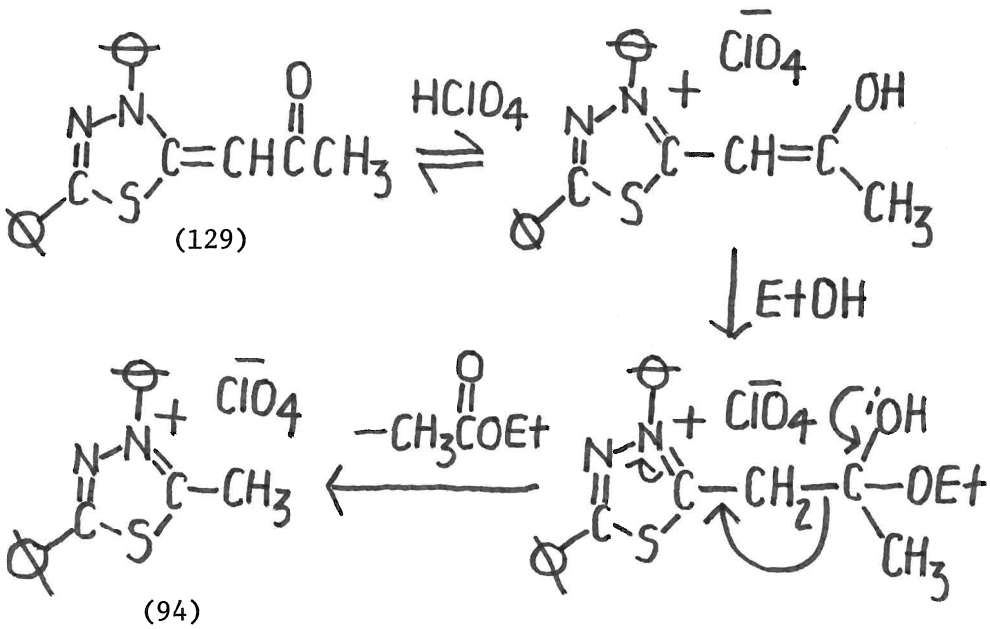
									
No.	R	Ar	R'	No.	R"	yield	m.p.	ν (C=O) cm^{-1}	p.m.r. of non-aromatic protons (δ)
69	CH_3		CH_3	126	H	69%	155-157°	1615	R'(CH_3), 2.12 R" (H), 5.45
69	CH_3	"	CH_2CH_3	127	H	63%	116-118°	1600	R'(CH_3CH_2), 1.13 (t), 2.41 (q), J = 7.2 Hz R"(H) 5.47
69	CH_2CH_3	"	CH_3	149	CH_3	74%	169-172°	1600	R'(CH_3), 2.25 R"(CH_3), 1.55
69	CH_2CH_3	"	CH_3CH_2	150	CH_3	93%	183-185°	1600	R'(CH_3CH_2), 1.17 (t), 2.52 (q). J = 7.0 Hz R"(CH_3), 1.55
69	CH_3	"		151	H	73%	168-170°	1595	R"(H), 6.16
72	CH_3		"	152	H	62%	169-170° (lit.[51] 170°)	1600	R"(H), 6.70
67			CH_3	129	H	65%	150-152° lit.[26] 152-153°	1600	R'(CH_3), 2.17 R"(H), 6.10

Satisfactory elemental analyses were obtained for all new compounds prepared and the spectral data were similar to those obtained by Callaghan and Vukov. The mass spectra all showed molecular ions in agreement with the proposed structures and the possible fragmentation mechanisms will be discussed subsequently.

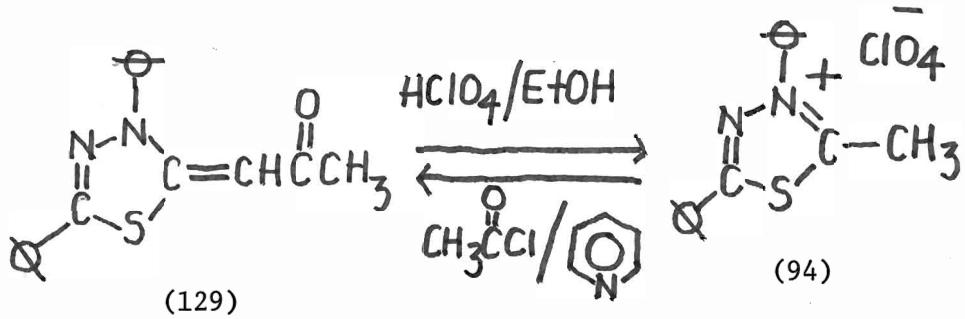
The compounds (129) and (152) had melting points in agreement with the literature values. Considering compound (129), it was found to



deacetylate when refluxed in perchloric acid/ethanol to give the 2-methyl perchlorate (94).

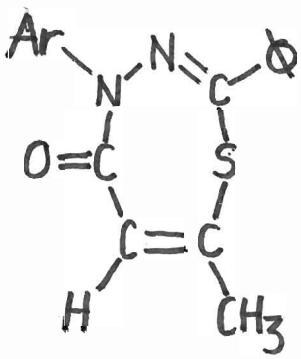


This nicely ties in with the previous section where enamine bases of the 2-methylthiadiazolium salts, (82) and (94), had been acylated using the appropriate acylating agents. These compounds, (126), (127) and (129), were found to be identical with those prepared by the reaction of the acetylated benzothiohydrazides with the appropriate acid anhydride. This would further confirm their structure and certainly the possible transformation between (129) and (94) would rule out the pyrazolone structure.

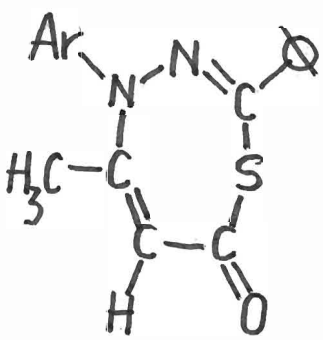


(129) (94)

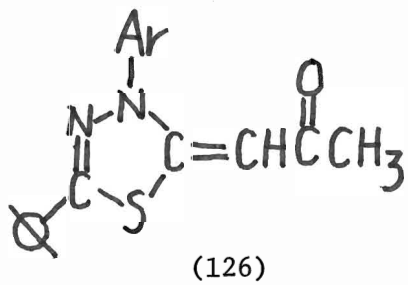
As mentioned previously, Elliott had reacted the benzothiohydrazide (68) with diketene and obtained a compound identical with that prepared by Callaghan. However, he favoured a seven-membered ring structure such as (153) or (154) rather than (126). This reaction was not



(153)



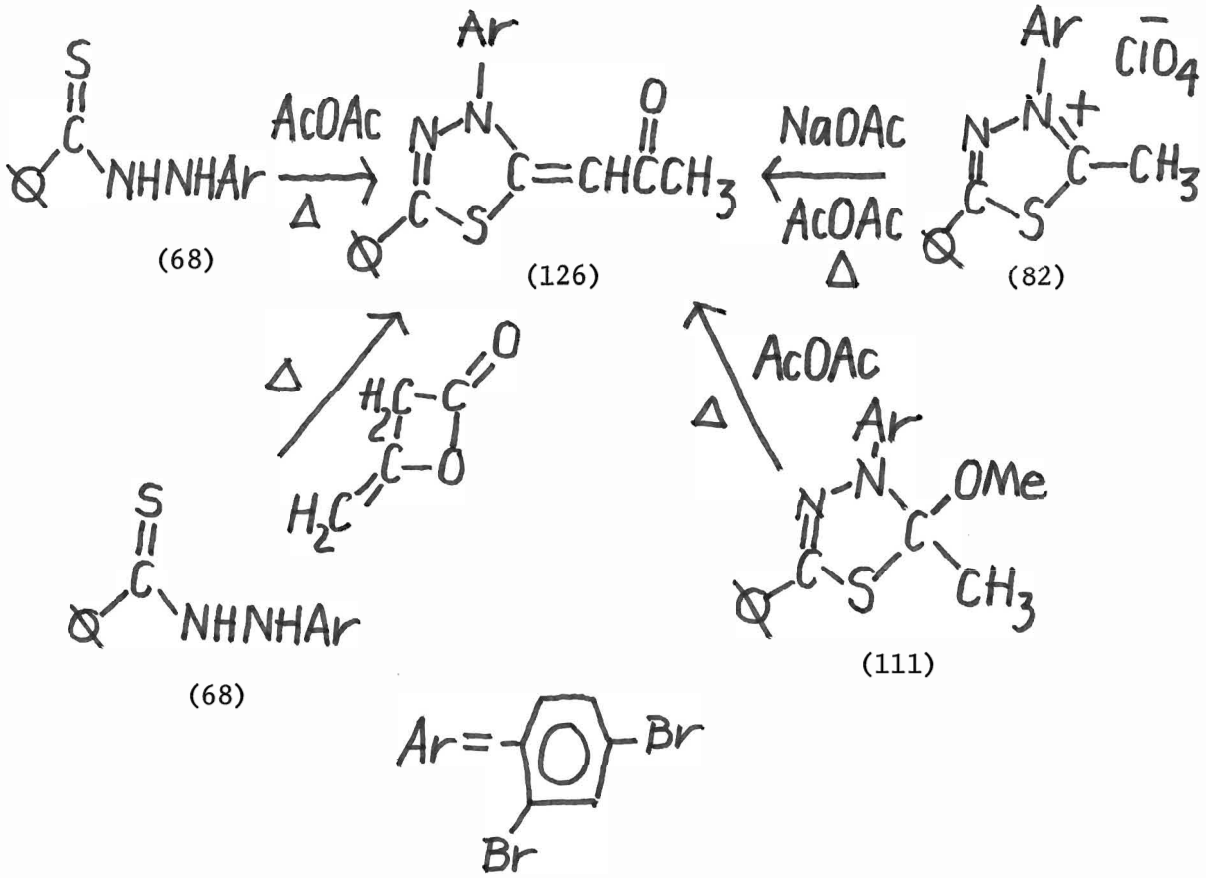
(154)



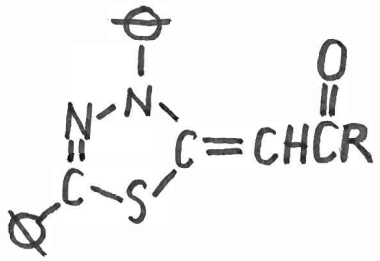
(126)

reported in the literature and therefore was repeated with the same results being obtained. The thiadiazapine structure is however somewhat doubtful since it would require a considerable amount of rearrangement in order to give the observed loss of ketene in the mass spectrum. It would also be difficult to reconcile the preparation of this compound from the enamine of the 2-methylthiadiazolium salt (82)1

The different routes leading to the acetonylidene compound (126) are summarized schematically below.



The mass spectra of the compounds (129) and (152) were examined in detail. The 3-(2,4-dibromophenyl) analogues exhibited a similar fragmentation but were more complex due to the loss of Br·.



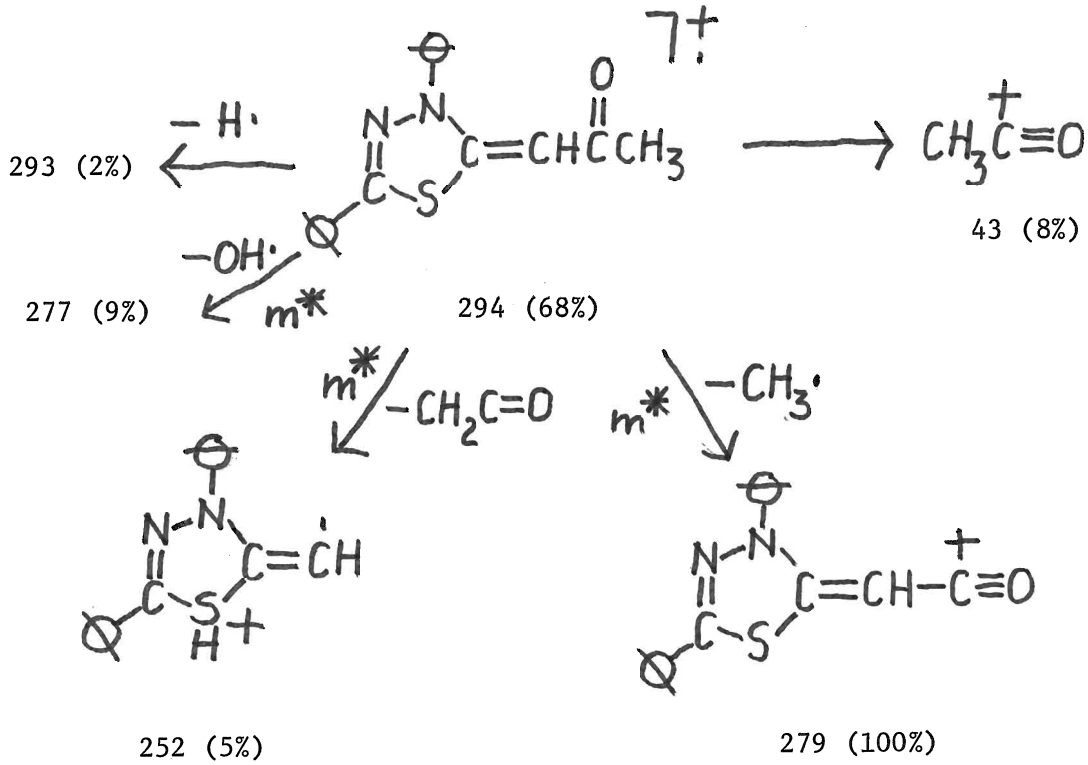
R

(129) CH_3

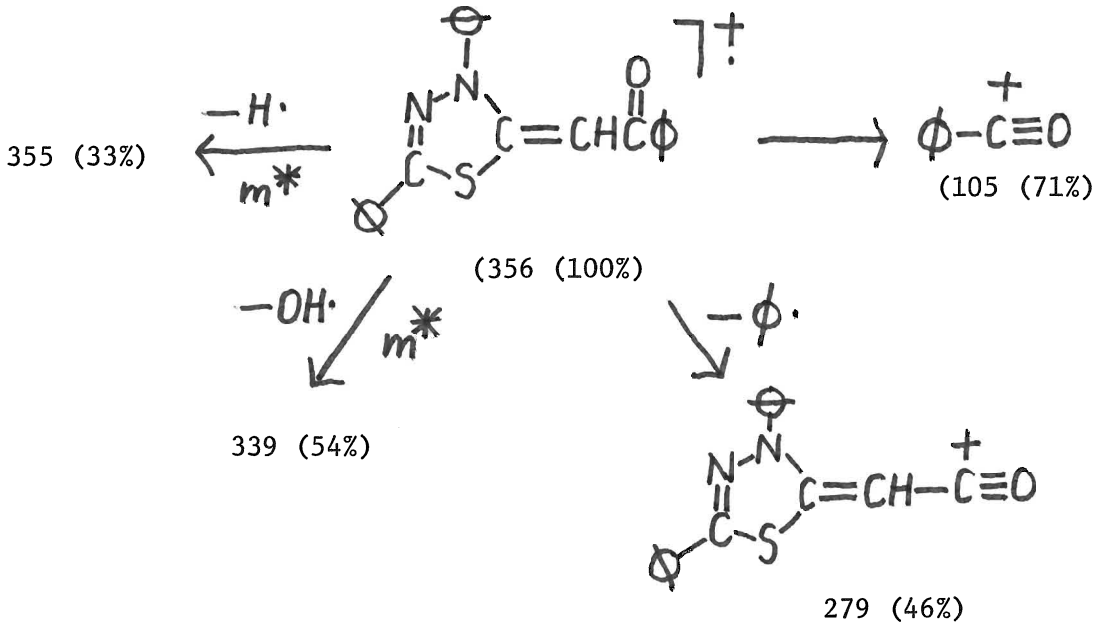
(152) ϕ

The initial fragmentation of compounds (129) and (152) is shown in Schemes 3 and 4 respectively. It should be pointed out that the structures proposed and fragmentations suggested without accompanying metastable transitions are hypothetical. There has only been one paper[55] published on the mass spectra of 1,3,4-thiadiazolines and because of the differences in substituents, it did not provide any useful analogues.

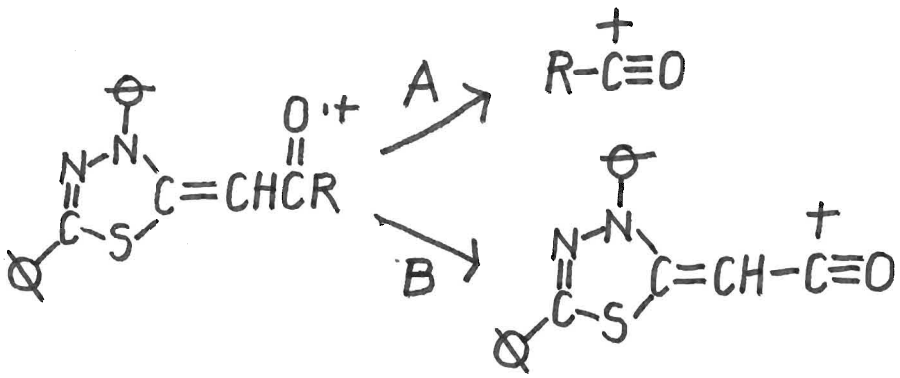
SCHEME 3



SCHEME 4

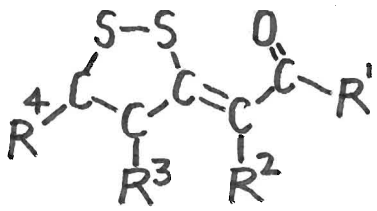


It appears that cleavage α to the carbonyl function is the most favoured process in the initial fragmentation. This can follow two routes as depicted below. The methyl analogue favours route B and the



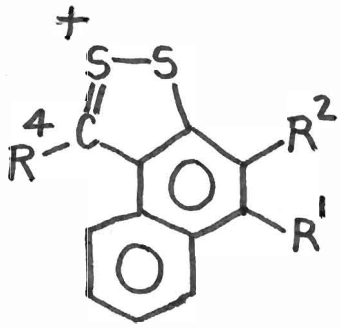
phenyl analogue route A. This is as would be expected regarding the relative stabilities of the ions formed.

The unusual feature of the initial fragmentation is the apparent loss of H• and OH• from the molecular ion, which seems to be especially favoured in the case of the phenyl analogue. A similar situation was observed[56] in the mass spectra of the α-(1,2-dithiole-3-ylidene) ketones (155) where interestingly the effect was only noticeable when R' = ϕ.

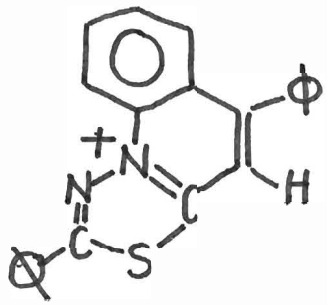


(155)

Through labelling experiments, it was shown that the hydrogen originated from the phenyl substituents, R^2 or R^3, or both if R^2 and R^3 were phenyl. The structure of the ion resulting from the loss of OH• was postulated as (156) when R^3 = phenyl. Presumably a similar effect is



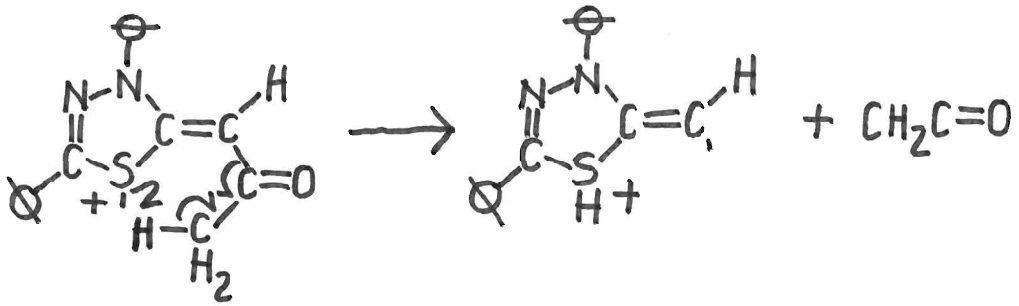
(156)



(157)

being observed for the thiadiazolines and the species (157) is formed. This would be supported by the fact that the 3-(2,4-dibromophenyl) analogue (151) exhibits this fragmentation to a much lesser extent.

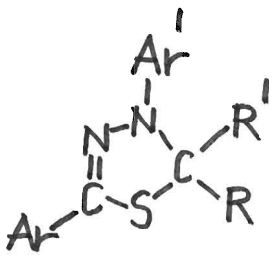
A point of difference between the phenyl and methyl analogues is the loss of ketene observed in the case of the methyl analogue. This was found to be a common feature of all the acetonylidene compounds prepared and could perhaps arise through hydrogen abstraction by an ionized ring sulphur (158).



(158)

The subsequent fragmentation, presumably arising from the ion at m/e 279, is shown in Schemes 5 and 6 for the methyl and phenyl derivatives respectively.

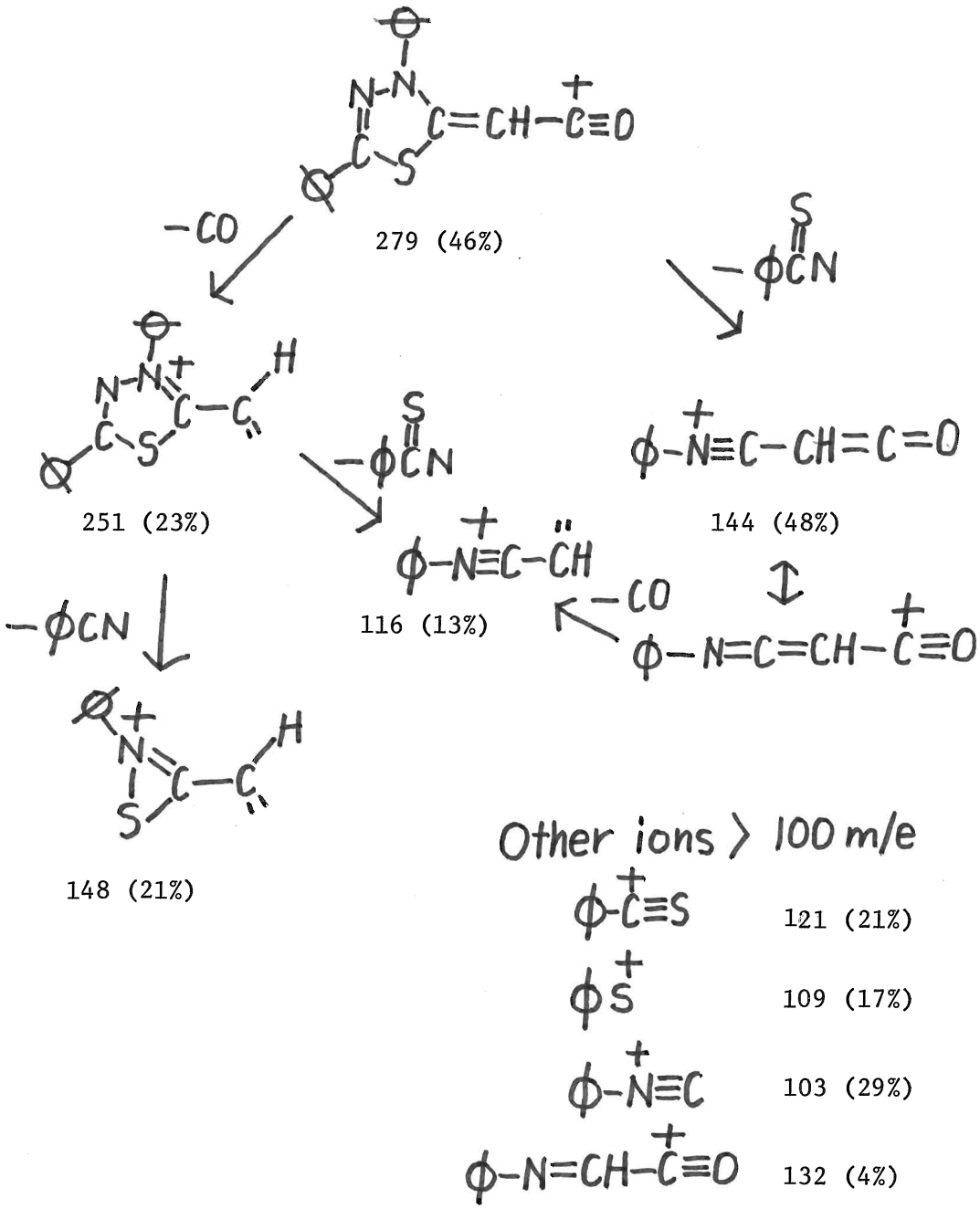
The loss of the thiobenzoyl nitrene seems to be the most favoured fragmentation for this ion, a metastable ion being observed in the case of the phenyl derivative. The presence of the thiophenol, thiobenzoyl and the benzoisonitrile ion was also observed by Wolkoff and Hammerum[55] in the fragmentation of (159).



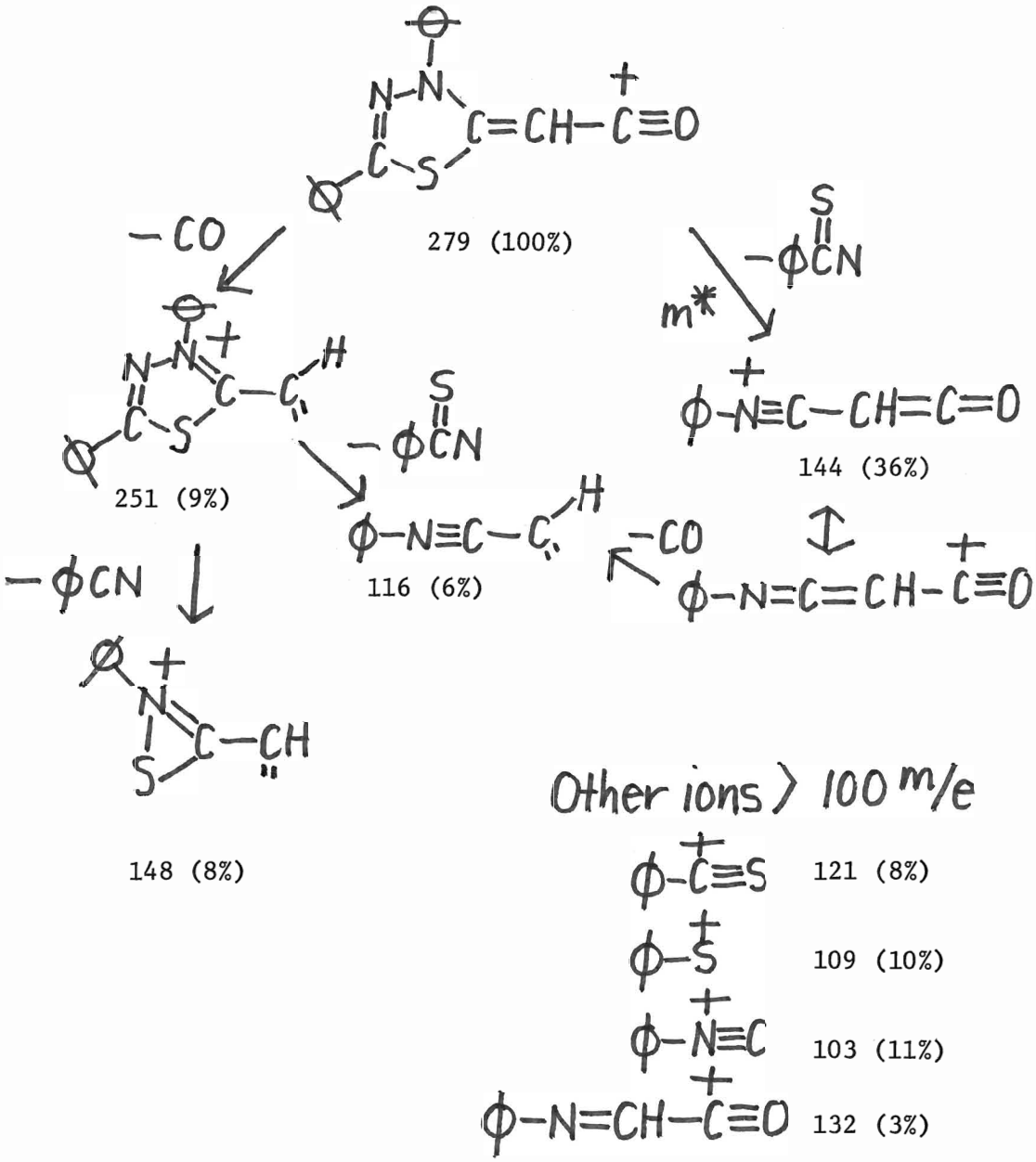
(159)

An attempt was made to prepare Barton's pyrazolone (146). The conditions employed were the same as those used to prepare antipyrine[57] (160) from 3 methyl-1-phenyl-5-pyrazolone (161). The pyrazolone in

SCHEME 5

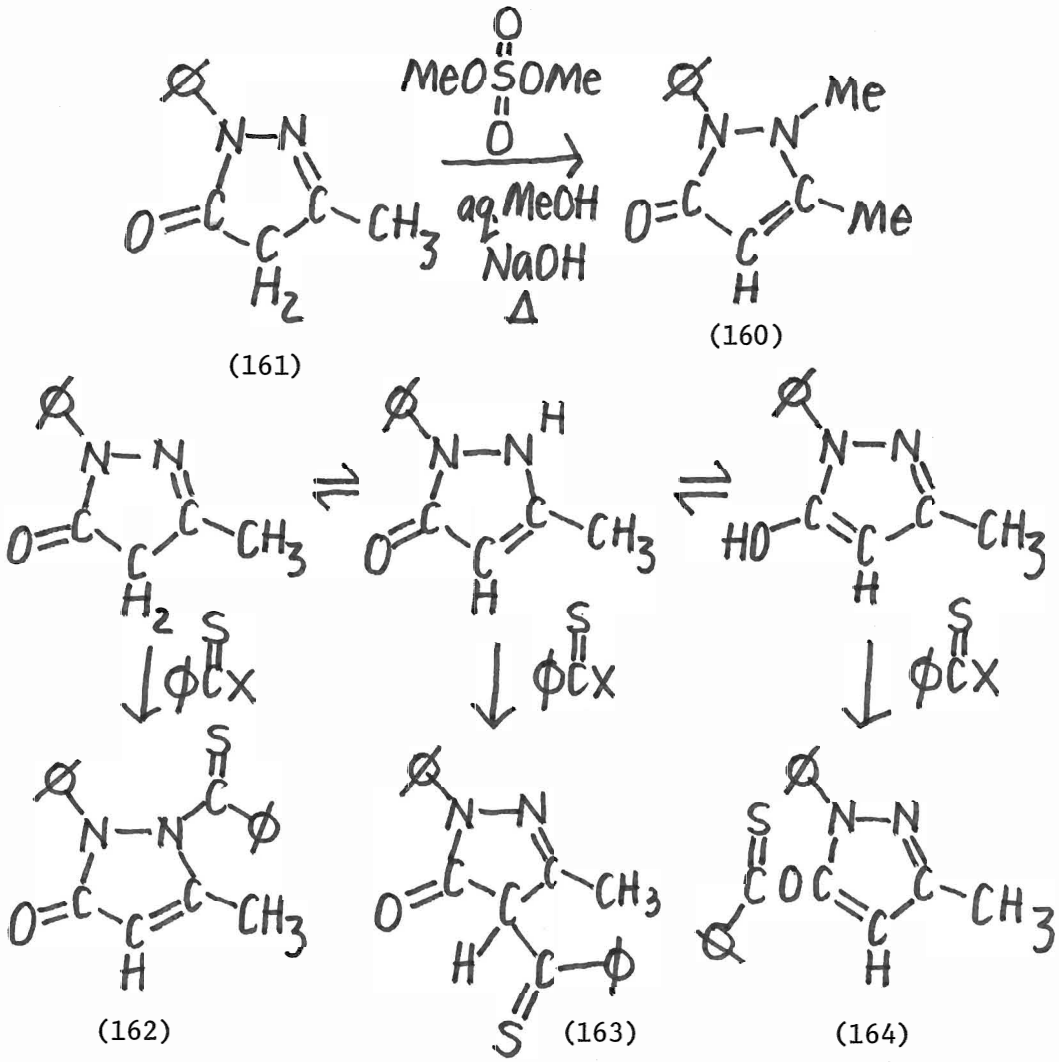

279 (46%)
−CO
−φCN
251 (23%)
144 (48%)
116 (13%)
148 (21%)
Other ions > 100 m/e
121 (21%)
109 (17%)
103 (29%)
132 (4%)

SCHEME 6

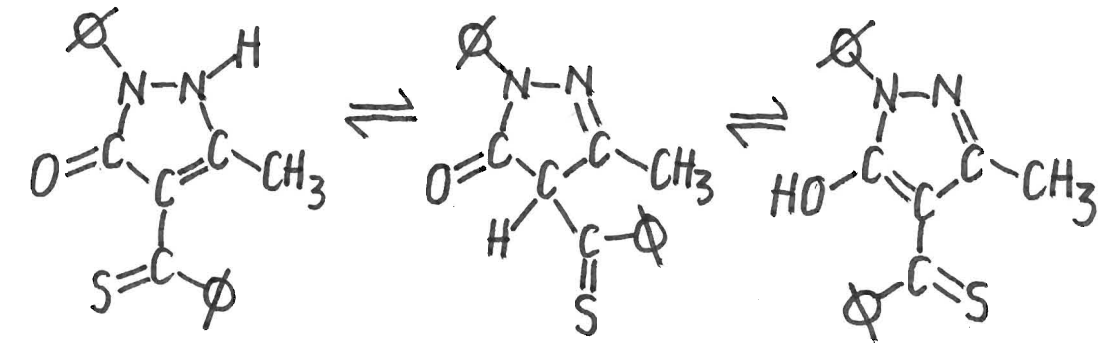

279 (100%)
-CO
-ϕCN
m*
144 (36%)
251 (9%)
116 (6%)
148 (8%)
Other ions > 100 m/e
121 (8%)
109 (10%)
103 (11%)
132 (3%)

aqueous methanol containing base, was heated with thiobenzoylthioglycolic acid (61). The product obtained gave a satisfactory elemental analysis for a thiobenzoyl derivative of (161). Its mass spectrum also showed the appropriate molecular ion; however the base peak corresponded to the loss of H· from this ion. The p.m.r. spectrum showed signals as would be expected for the methyl and phenyl portions of the molecule but the expected "olefinic" proton appeared as a broad singlet at 14.16 δ which disappeared on addition of deuterium oxide. The infrared spectrum did not show either C=O, O-H or S-H absorption.

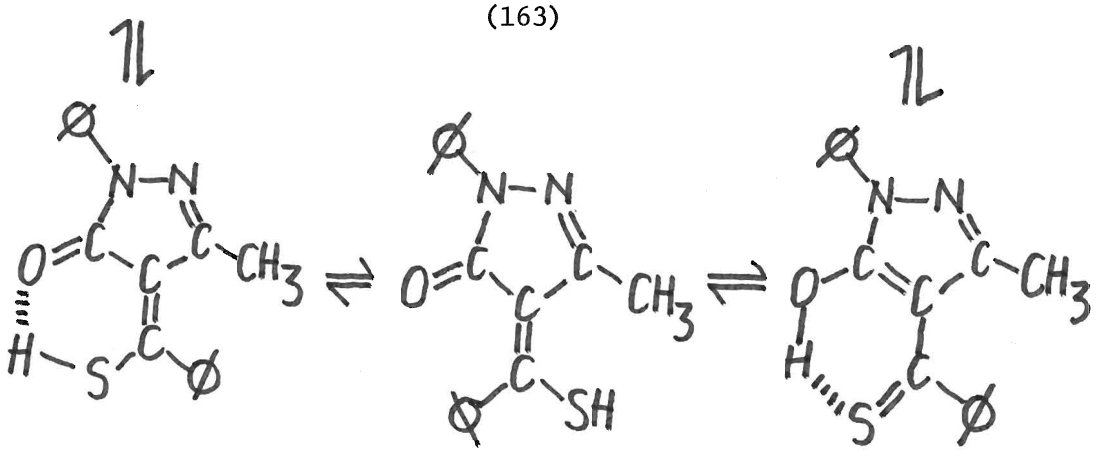
It should be noted that the pyrazolone (161) is capable of considerable tautomerism[57] and that products from N (162), C (163) and O (164) thiobenzoylation could be obtained.



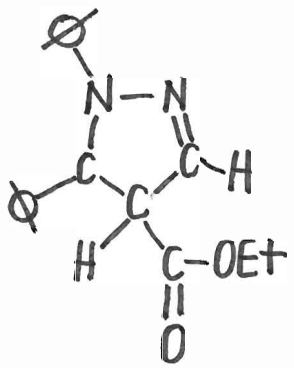
On the basis of the spectroscopic data, it is suggested that the material obtained is the C-thiobenzoylated derivative (163). This compound besides being capable of the usual pyrazolone tautomerism would also be expected to exhibit the tautomeric properties of monothio-β-dicarbonyl compounds[58]. The possible tautomers are shown below.



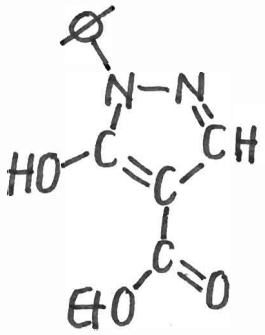
(163)



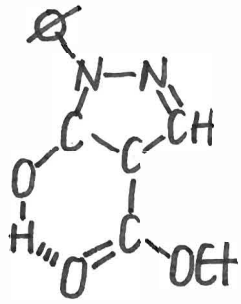
The only definite conclusions[59] drawn about the tautomerism of 4-acyl- and 4-thioacylpyrazol-5-ones concern the 4-alkoxycarbonyl derivatives (166). These exist in the free form (167) (favoured by basic solvents which can break down the intramolecular hydrogen bonding and stabilize the free OH by intermolecular hydrogen bonding) and the chelated form (168).



(166)

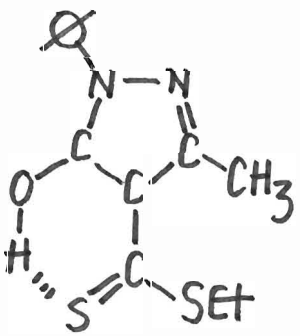


(167)



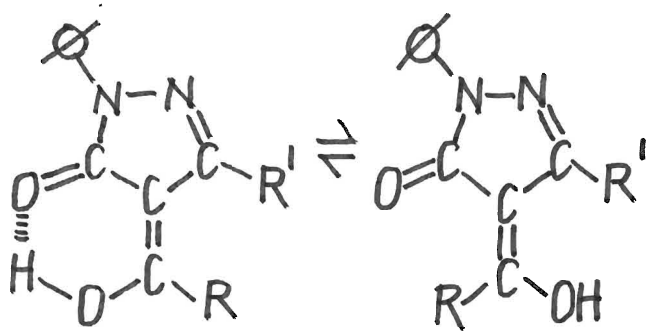
(168)

The sulphur analogue (169) because of the absence of a carbonyl stretch and the presence of an intramolecularly bonded OH band was thought to behave similarly.



(169)

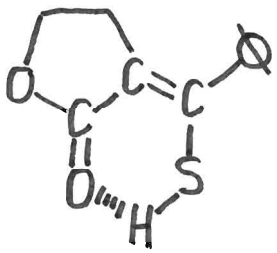
The situation is less clear for 4-acylpyrazolones, but it is felt that they exist predominantly in the forms (170) and (171). The



(170) (171)

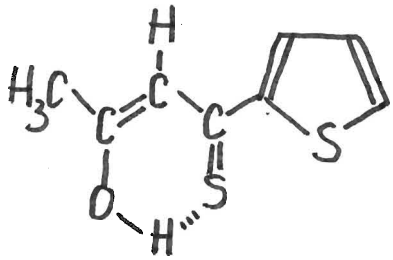
apparent difference between the acyl and alkoxycarbonyl derivatives is thought to parallel the nonenolization of the ester carbonyl in β-keto esters.

Compounds analogous to (164) have been prepared and studied by Duus and coworkers[60]. The derivative (172) exists entirely in the cis-enethiol form. The p.m.r. ($CDCl_3$) showed the hydrogen bonded thiol proton at 7.28 δ and the infrared ($CHCl_3$) showed the carbonyl band at 1701 cm^{-1} and the SH absorption at 2432 cm^{-1}. This is quite unlike the data observed for the pyrazolone (163) where the hydrogen bonded proton is shifted twice as far downfield and the carbonyl and SH bands are not observed. Admittedly, potassium bromide discs are not the best medium for examining broadened SH or OH



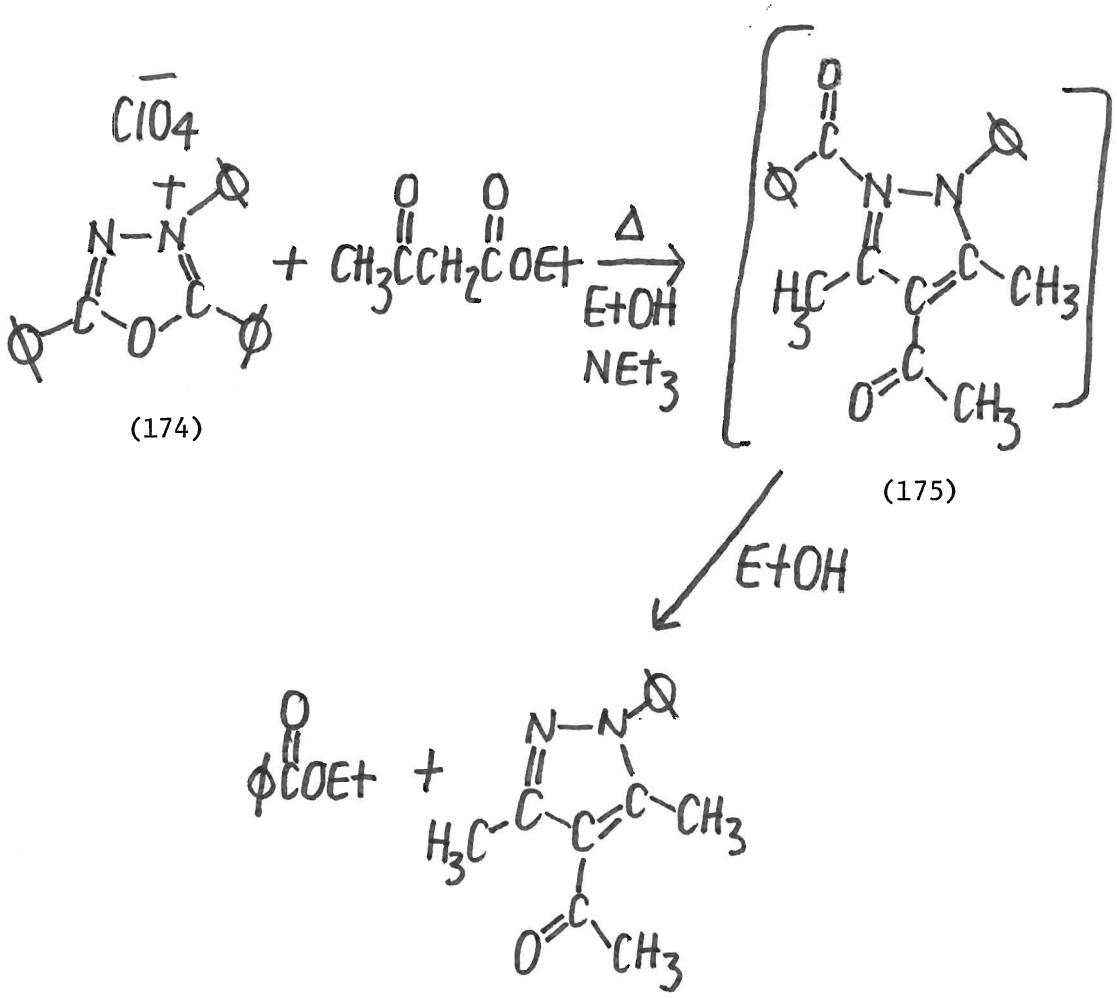
(172)

absorptions and the infrared spectrum should be reexamined using liquid cells. Compounds (173) analogous to (165) have also been examined[62] and are thought to exist in the cis-enol form. Unfortunately



(173)

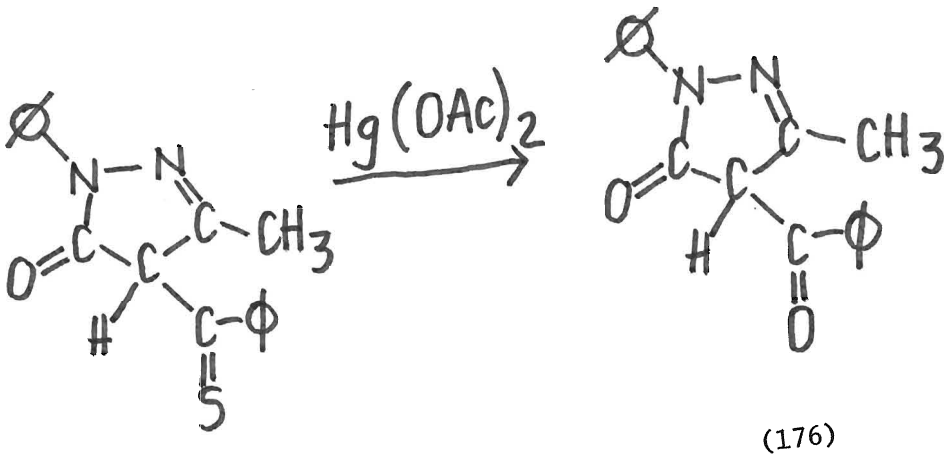
infrared data were not given. The OH proton signal was found to lie at 15.48 ppm and exhibited weak coupling with the methyl protons. The chemical shift is certainly closer to that observed for the pyrazolone and therefore, the available data suggest structure (165) although extremely strong hydrogen bonding (which a chemical shift of 14.16 δ suggests[61]) in (164) could shift the carbonyl stretching frequency below 1600 cm^{-1} and also broaden the SH band such that it is not observed. Actually it is extremely doubtful that Barton's pyrazolone could be obtained by this method since it would probably function as a thiobenzoylating agent. Boyd and coworkers[10] noted a similar effect in the reaction of the oxadiazolium salt (174) with ethylacetoacetate. The intermediate N-benzoylpyrazole (175) could not be obtained since it rapidly transferred the benzoyl group to the solvent.



(174)

(175)

Ignoring the tautomerism, the identity of the 4-thiobenzoyl pyrazolone (165) could be confirmed by oxidizing it to the known[63] 4-benzoyl pyrazolone (176).



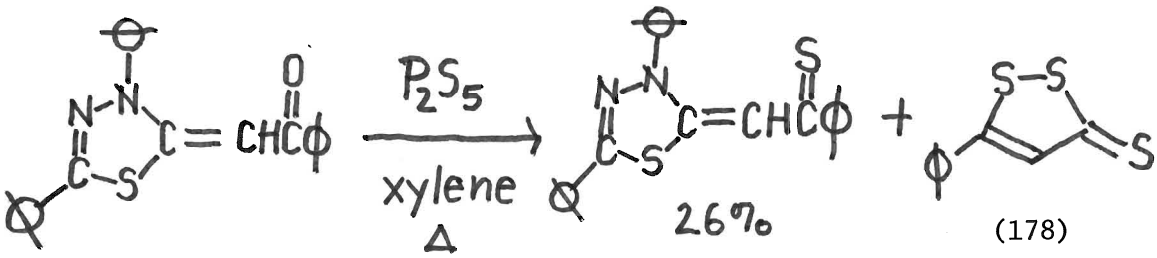
(165)

(176)

THIOACYL DERIVATIVES OF THE ANHYDROBASE

Since Testę and coworkers[51] had demonstrated the possibility of interconversion of the thioacetophenonylidene compound (140) and its oxygen analogue (141), it was decided to see if the other ketonylidene compounds prepared in the previous section would behave similarly.

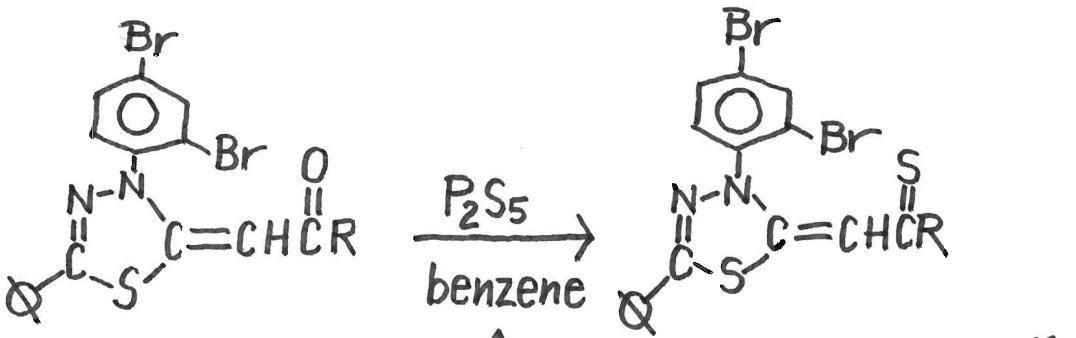
The conversion of (152) to (177) was first repeated using the procedure described[51]. As had been noted, the reaction went with the accompanying formation of the 1,2-dithiol-3-thione (178). This



(152) (177) (178)

material had an R_f value very close to that of the thiocarbonyl compound (177) and they therefore eluted together when chromatographed. However, the mass spectrum of the mixture showed an ion (m/e 210) which presumably corresponded to this species. When the mixture was crystallized, (178) was found to remain in the mother liquor and a mass spectrum of the thiocarbonyl compound which had a melting point in agreement with that reported[51], did not show an ion corresponding to (178).

Compounds (126) and (151) were treated similarly but in this instance, benzene was used as a solvent and the reflux period was shortened. The thiocarbonyl compounds (117) and (128) were obtained in a much higher yield and the formation of the 1,2-dithiol-3-thiones



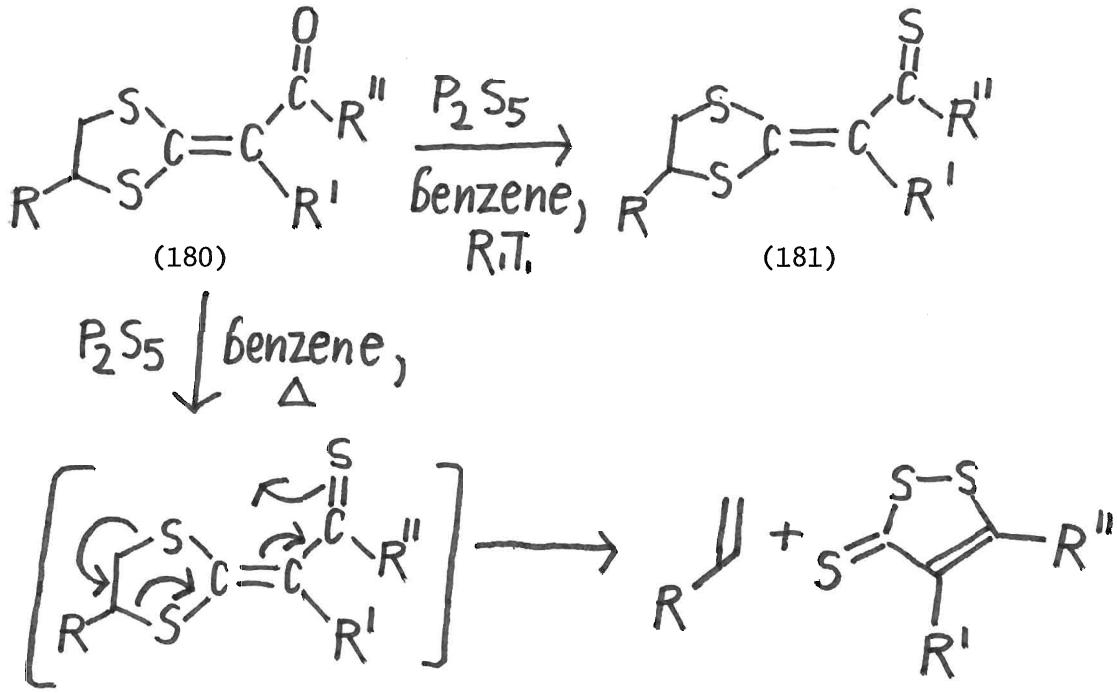
(126) R=CH_3

(151) R=φ

(117) R=CH_3 73%

(128) R=φ 68%

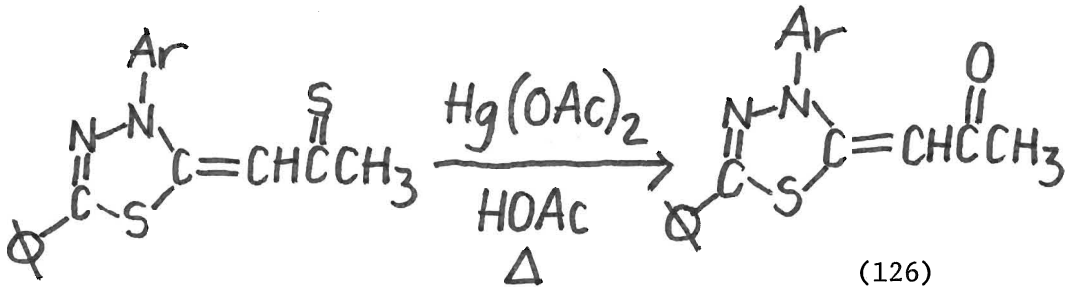
was not observed. This is presumably due to the milder conditions employed. A somewhat similar situation was observed[64] in the conversion of the ketone (180) to the sulphur analogue (181) which



required exceptionally mild conditions.

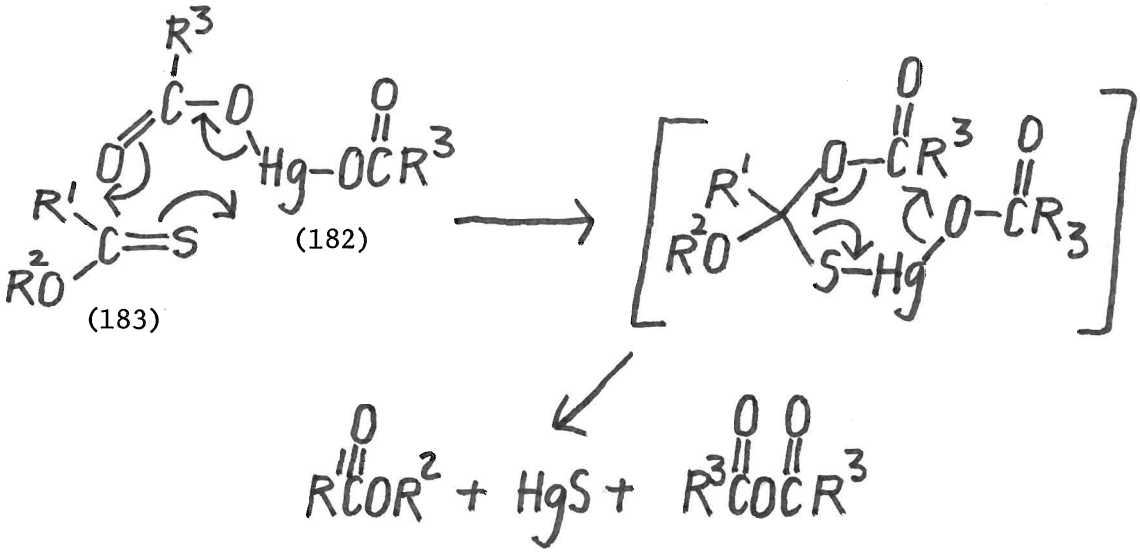
The thioaceto phenonylidene derivative (128) was found to be identical with that prepared by the thiobenzoylation of the anhydrobase of the 2-methyl-thiadiazolium salt (82).

To confirm the identity of the thioacetonylidene derivative (117), it was reacted with mercuric acetate and the carbonyl compound obtained was found to be identical with the acetonylidene compound (126).



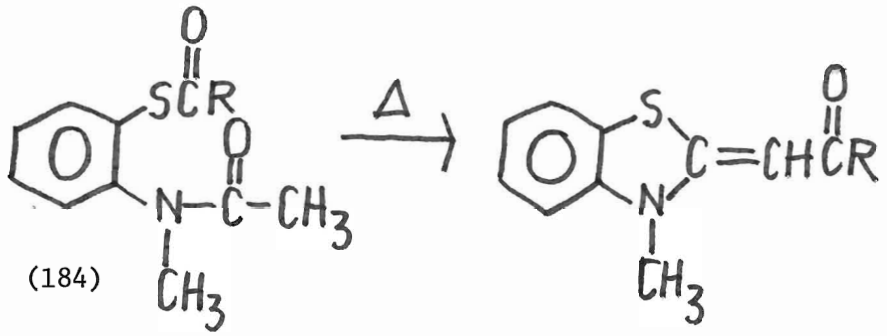
(117) (126)

The mechanism of this desulphurization reaction is probably the same as that reported[65] for the synthesis of acid anhydrides employing mercuric carboxylates (182) and thionoesters (183).



The p.m.r. and mass spectra of these compounds will be discussed subsequently.

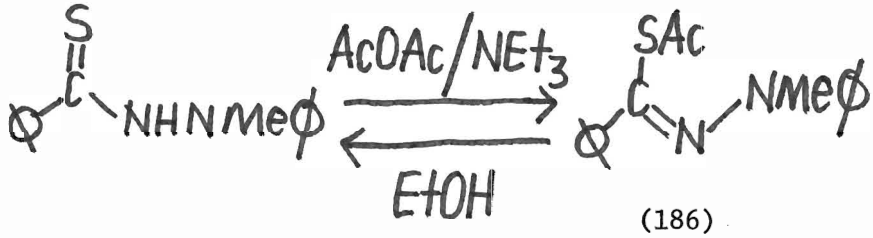
Upon considering other routes which may give rise to the acetonylidene thiadiazoline, the work of Dénes and his group[66] was considered. They showed that diacyl-p-aminothiophenols (184) lost water on melting to give the corresponding benzothiazolines (185). The mechanism of this reaction is however uncertain, since crossover



(184) (185)

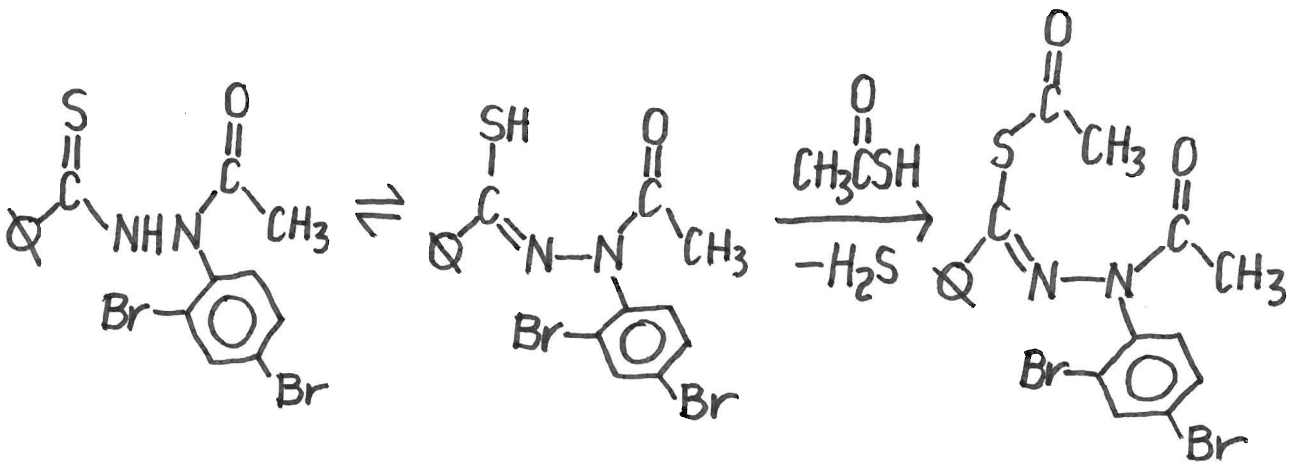
experiments showed that the reaction went with intermolecular transfer of the S-acyl group.

Since Elliott[67] had difficulty in preparing the S-acetyl derivative (186) by conventional methods it was decided to prepare



(186)

the S-acetyl derivative (187) by reacting thioacetic acid with the N'-acylbenzothiohydrazide (69) since it has been shown[68] that this

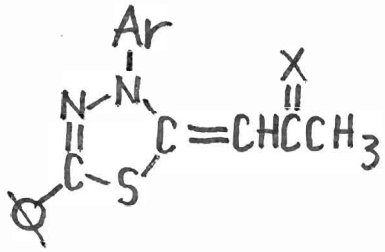


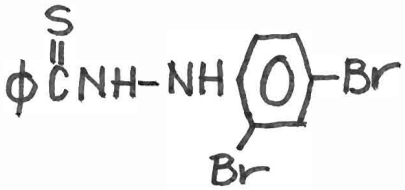
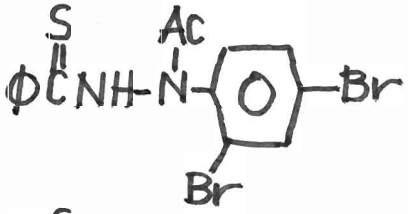
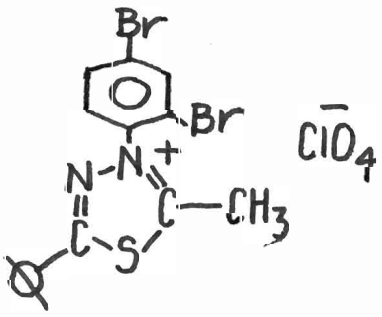
(69) (187)

reagent acetylates thiols at room temperature and the excess acid can be removed under reduced pressure leaving behind a product of analytical purity.

Unfortunately, when a suspension of (69) in excess thioacetic acid was stirred for 24 h, a reaction did not appear to occur (t.l.c.). However, when the suspension was heated such that (69) went into solution, compounds (126) and (117) were obtained. Similar treatment of (67) and (68) gave analogous products and the anhydrobase generated from the salt (82) was found to behave in the same fashion although the oxygen analogue (126) (observed by t.l.c.) was not isolated due to the presence of various by-products with similar R_f values. The results are summarized in Table 7.

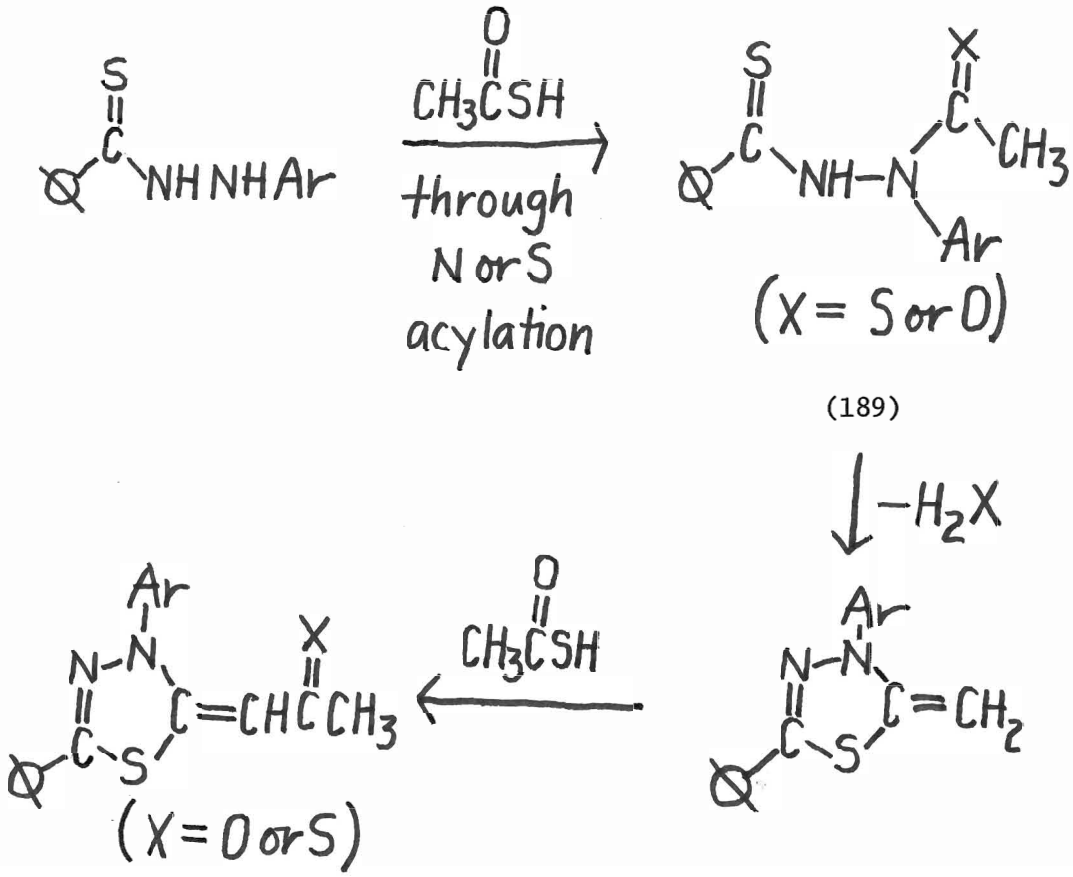
TABLE 7



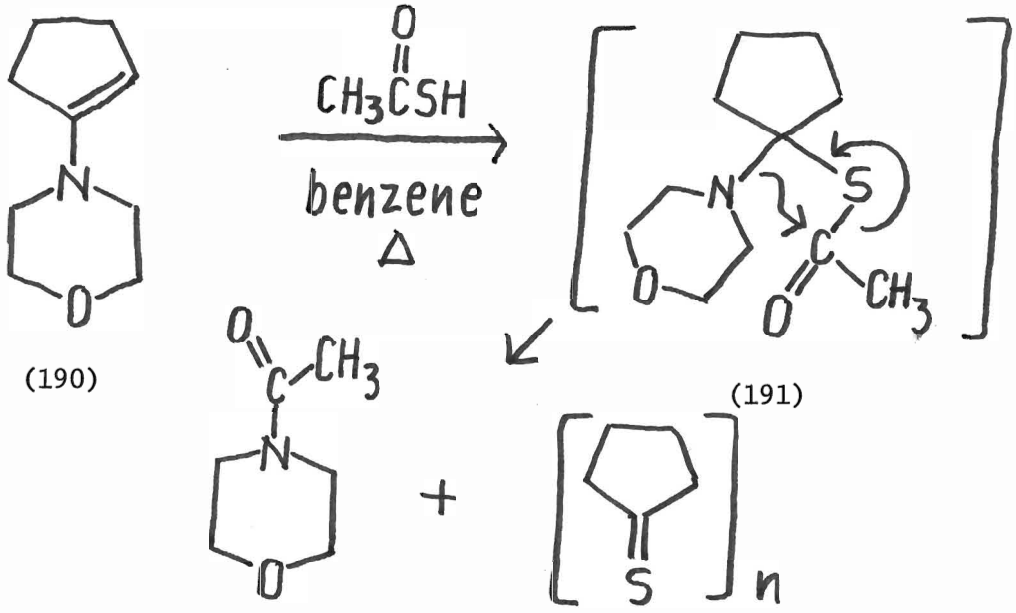
			X = S	X = O
(68)		CH_3CSH, Δ	(117) 59%	(126) 24%
(69)		CH_3CSH, Δ	(117) 52%	(126) 15%
(67)		CH_3CSH, Δ	(188) 78%	(129) 5%
(82)		CH_3CSH, $NEt_3/EtOH$, Δ	(117) 48%	(126) (t.l.c.)

This reaction was not further examined but on the basis of the above experiments, it appears that thioacetic acid functions both as an acetylating and a thioacetylating agent. Remaining within the framework of the mechanism proposed for the formation of the acetonylidene compound (134) when the benzothiohydrazide is refluxed in acetic anhydride, one would expect the reaction to follow Scheme 7.

SCHEME 7



The nature of X in the intermediate (189) is not known but could perhaps be determined by reacting the benzothiohydrazide with an equivalent of thioacetic acid. However it is apparent that the N'-acetylbenzothiohydrazide is capable of undergoing this reaction. The preference for thioacetylation of the anhydrobase is unusual in that thioacetic acid is considered an acetylating agent. Support for this aspect of the mechanism could not be found in the literature. The only reference found regarding the reactions of thioacids with enamines is by Lawesson and coworkers[69]. They found thioacetic acid to add across the C=C of the enamine (190) to give the intermediate (191) which was very unstable and decomposed to the amide (192) and the thione (193).

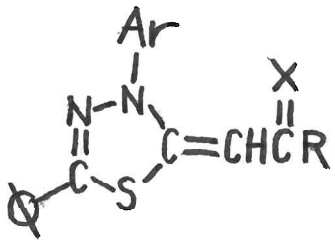


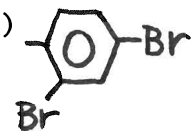
(190) (191)

(192) (193)

The p.m.r. data for the non-aromatic protons of the thioketones and their respective oxygen analogues are shown in Table 8.

TABLE 8

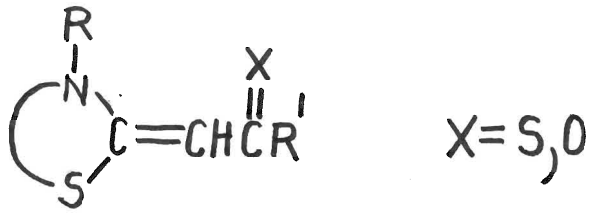


	Ar	R	X	δ (ppm) CH_3		δ (ppm) H	
(117)		CH_3	S	2.70	Δδ = 0.58	6.60	Δδ = 1.15
(126)	"	"	O	2.12		5.45	
(128)	"	φ	S	--		7.03	Δδ = 0.87
(151)	"	"	O	--		6.16	
(188)	φ	CH_3	S	2.67	Δδ = 0.5	7.01	Δδ = 0.91
(129)	"	"	O	2.17		6.10	
(177)	"	φ	S	--		(7.13-8.03)*	
(152)	"	"	O	--		6.70	

* buried in the aromatic region

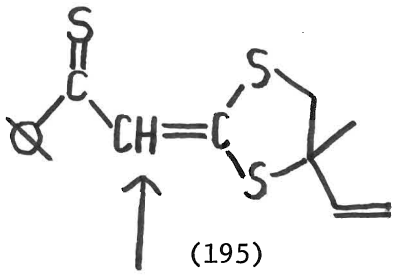
It has been demonstrated[70] that the thiocarbonyl group is much more effective in the deshielding phenomenon than the carbonyl group but exhibits the same coordinate susceptibilities as the carbonyl group. That is, protons in the plane of the thiocarbonyl group experience deshielding and those above the plane experience shielding.

This effect is clearly observed for the thiocarbonyl compounds prepared where a downfield shift of approximately 1 ppm is observed for the olefinic protons and 0.5 ppm for the methyl protons. Unfortunately, although a large variety of compounds containing the structural unit (194)



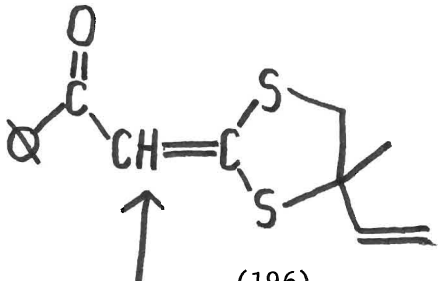
(194)

have been prepared, there do not seem to be any p.m.r. data given with which a direct comparison could be made. The chemical shift difference between compounds (195) and (196) is of a similar magnitude.



(195)

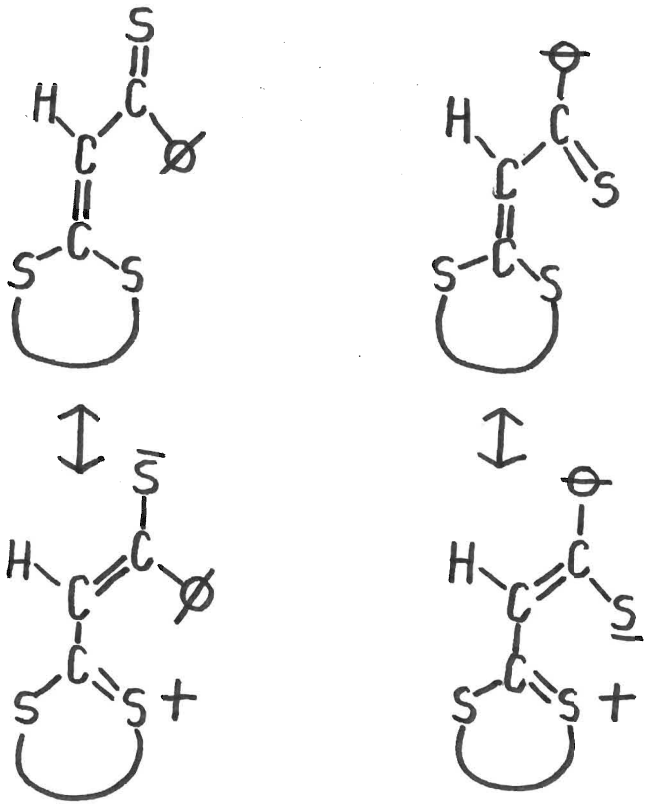
δ = 7.86 and 7.90



(196)

δ = 7.16

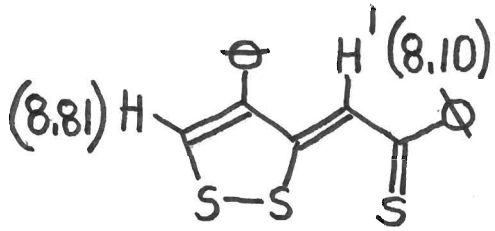
(197) (198)



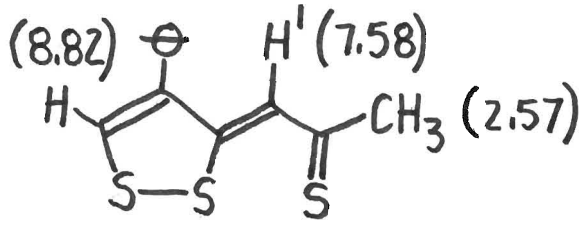
(199) (200)

The apparent doublet observed for the olefinic proton in (195) was thought to be due to the existence of the two conformational isomers (197) and (198) which are presumably in a planar conformation because of the important resonance contributions of (199) and (200).

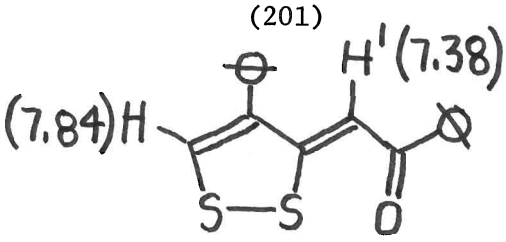
Another series of compounds where the chemical shifts resulting from sulphur-oxygen exchange were examined[71] are the thiothiophthenes, (201) and (202), and their oxygen analogues, (203) and (204). The



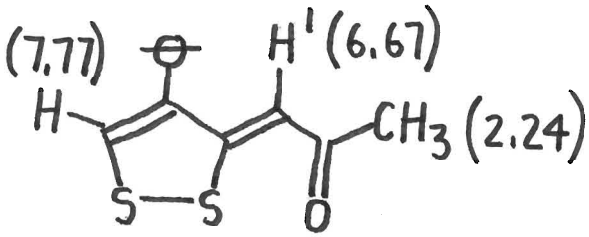
(201)



(202)

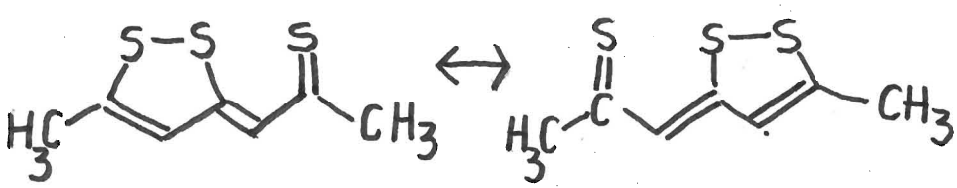


(203)

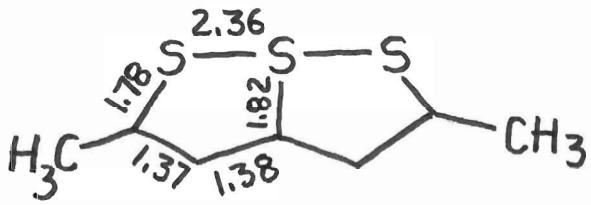


(204)

chemical shifts of the non-aromatic protons are shown in parentheses. Again the shifts are of the same order as observed for the compounds prepared. This is particularly interesting since the chemical shift differences of the oxygen and sulphur analogues (0.96-1.07 for the olefin proton, H') were regarded as evidence of a greater ring current and aromaticity in the thiothiophthenes. It should be noted that the thiothiophthenes exhibit a so-called no-bond resonance[72], (205) and (206), the molecule being planar and symmetrical about the center carbon-sulphur bond (207). The oxygen analogues (208) are thought to

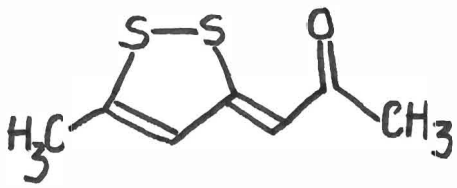


(205) (206)



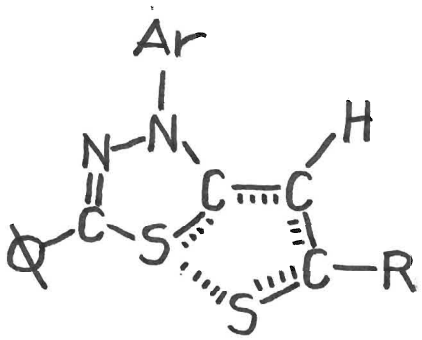
(207)

exhibit a similar interaction but to a much lesser extent[71].



(208)

It is therefore tempting to suggest that a similar effect is being observed for the thiadiazoline analogues and that some of the electron density drawn out of the ring is being donated back through the ring sulphur (209). There are however insufficient data to support this.

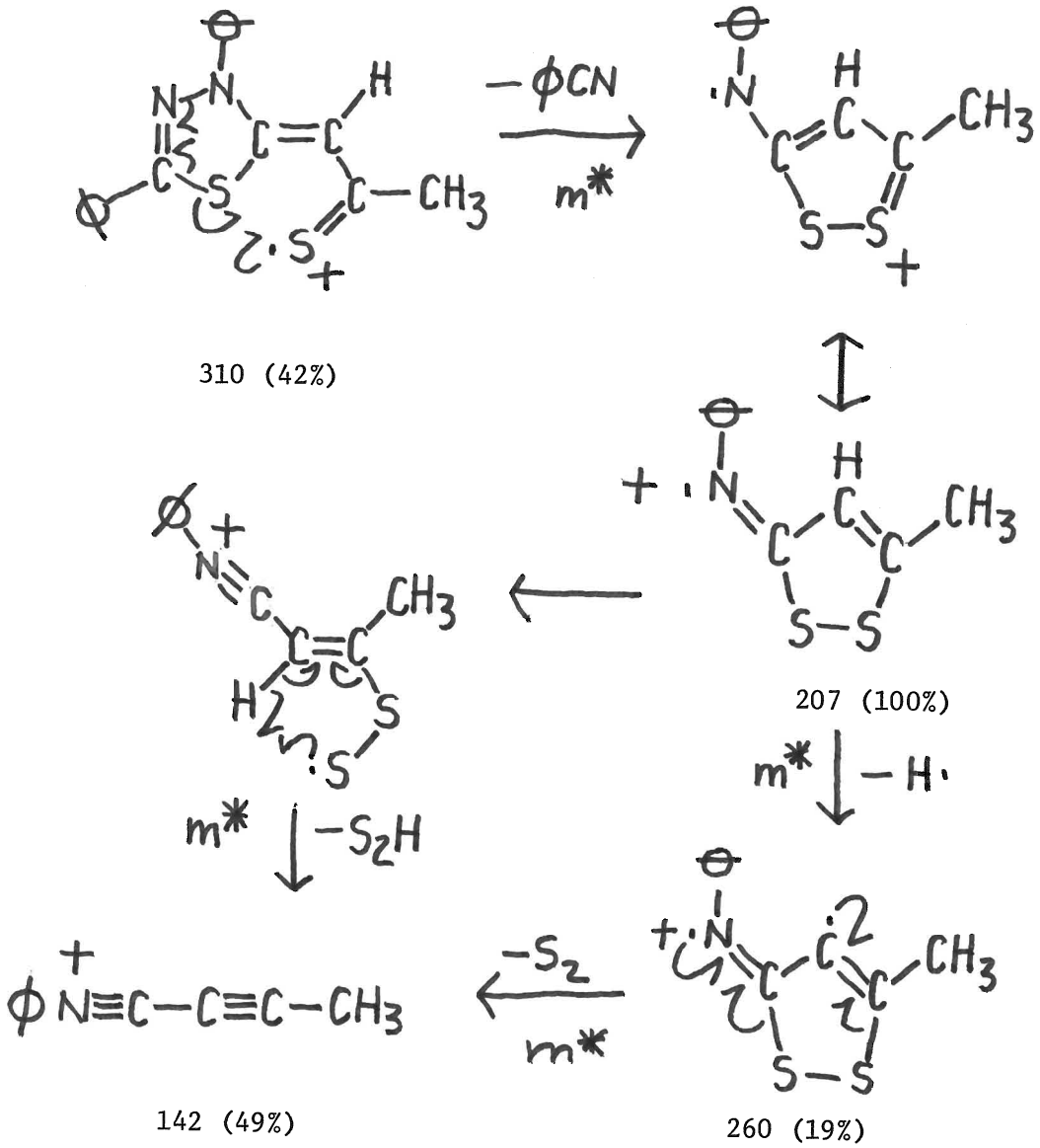


(209)

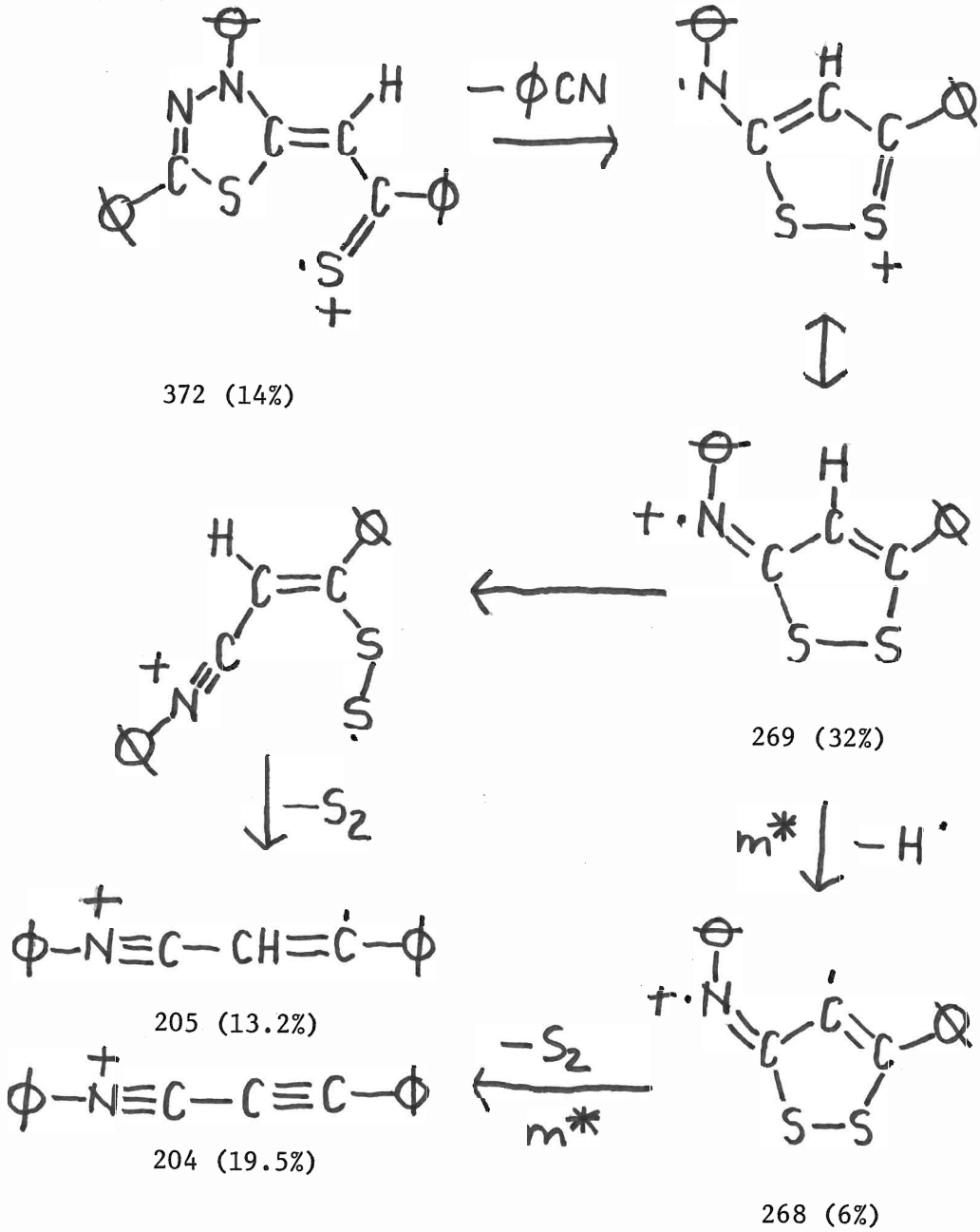
It can also be seen that the thiothiophthenes did not exhibit the type of isomerism as noted for (195) but this is not unexpected in view of the "no bond resonance". The few thiadiazolines prepared also did not appear to exhibit this isomerism and therefore seem to favour one conformation, although the available data do not allow one to identify it.

The mass spectra for the thiones, (188) and (177) are shown in Schemes 8 and 9 respectively.

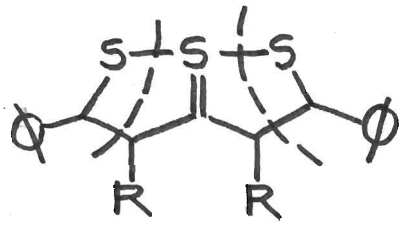
SCHEME 8



SCHEME 9



As can be seen, the spectra of these compounds are radically different from their oxygen analogues. Presumably ionization of the thioketone sulphur occurs and the formation of an S-S bond brings about the loss of benzonitrile. A somewhat similar effect was noted in the mass spectra of thiothiophthenes (210)[73] but in this instance, the ion

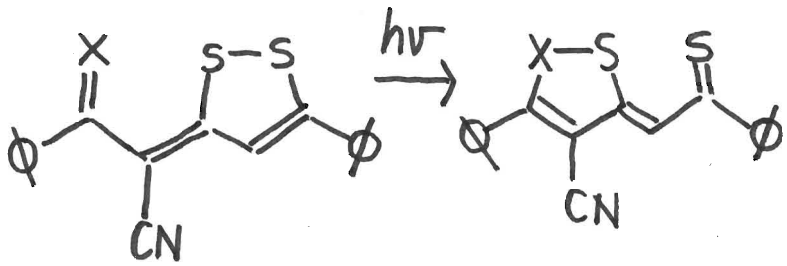


(210)

ϕ-C≡S$^+$ was observed.

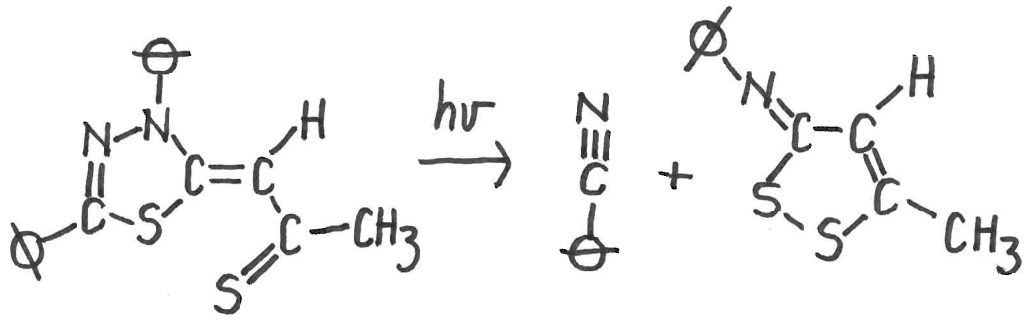
The dithiole ion then appears to break down through the loss of S_2 or S_2H.

Ring formation in analogous systems[74] (211) have been induced photolytically and it would perhaps be of interest to subject the



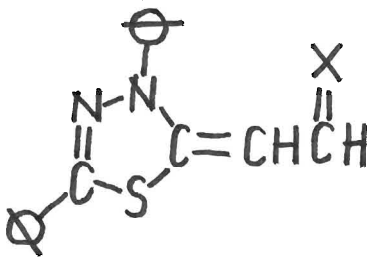
(211) X= Nφ, O

thiadiazoline compounds to these conditions since there seems to be an interaction between the ring sulphur and the thiocarbonyl sulphur. On the basis of the mass spectral fragmentation and the reaction of (211), one would expect (212) and benzonitrile to be formed.



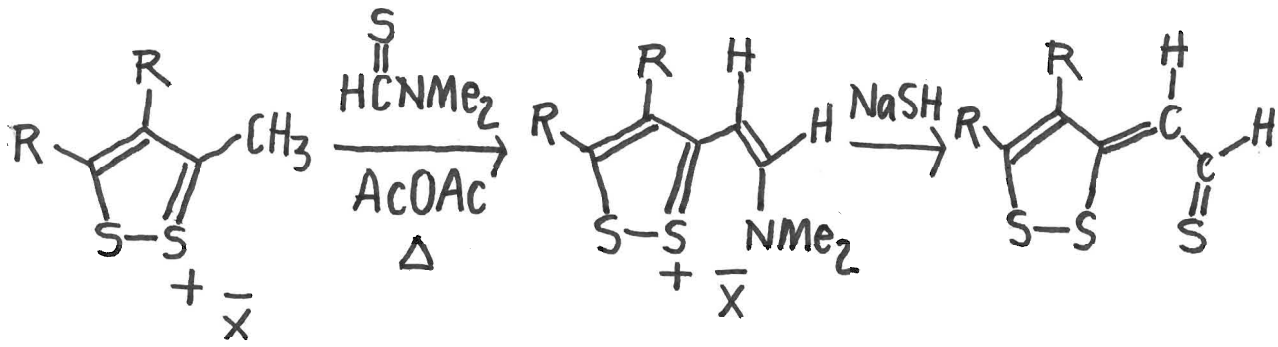
(212)

It would have been interesting to have been able to include the aldehydes (213) and (214) in the foregoing spectral discussions.



(213) X=S (214) X=O

However, due to lack of time, their syntheses were not attempted although it was noted that there existed a good analogy between the chemistry of 3-methyl-1,2-dithiolium salts (215) and the 2-methyl-thiadiazolium salts. Reid[71] and coworkers have shown that these salts readily condense with dimethyl thioformamide to give the salts (216)

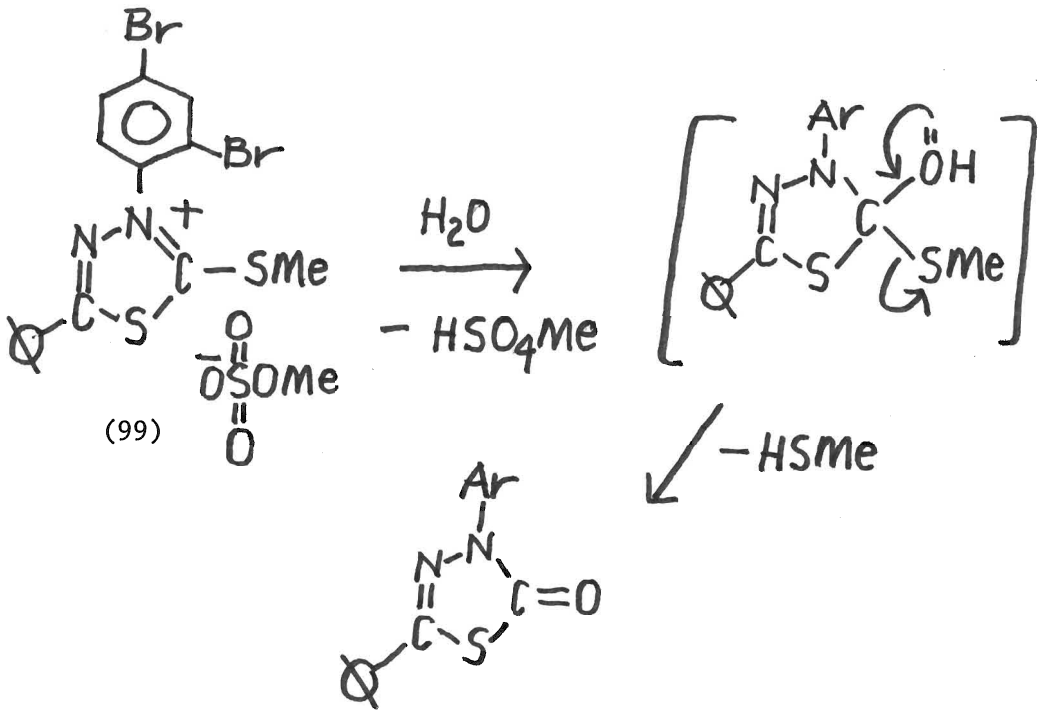


(215) (216) (217)

which in turn react with nucleophiles such as sodium hydrogen sulphide to give the thioaldehyde (217). This is quite similar to the condensation of the 2-methylthiadiazolium salt (82) with p-dimethylaminobenzaldehyde to give the styryl dye (124) and one would expect that Reid's method could be applied to prepare (213) and (214).

REACTIONS OF 2-METHYLTHIO-1,3,4-THIADIAZOLIUM SALTS

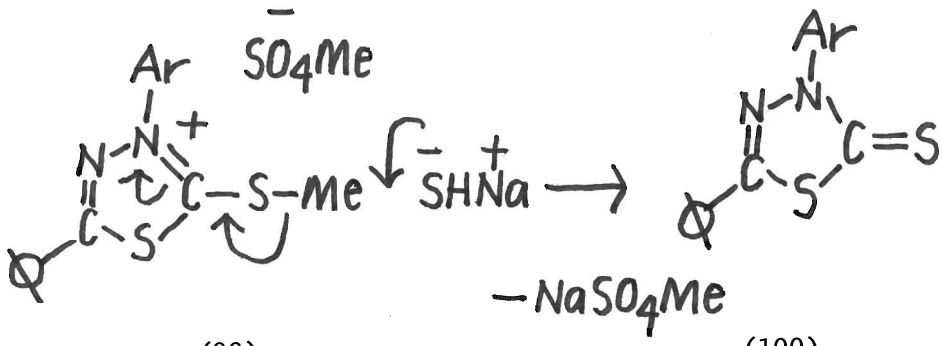
As previously mentioned, the methosulphate (99) was found to be quite hygroscopic. A suspension of the salt stirred for 24 h in water was found to decompose to the ketone (218). This was found to be



(99)

(218)

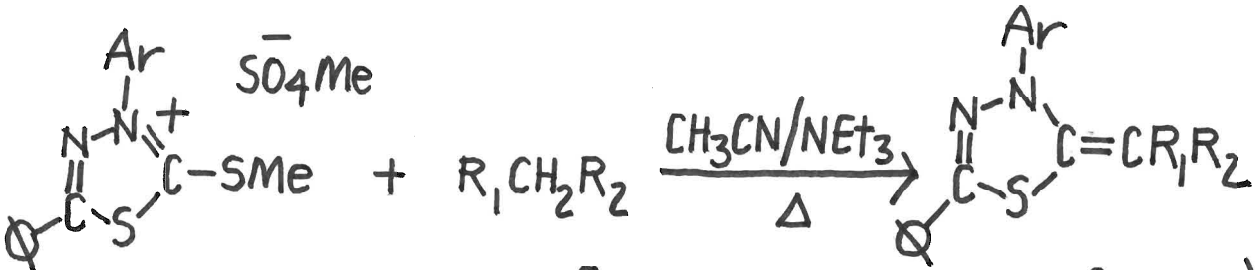
identical with an authentic sample prepared by the method of Pawelchak[75]. A similar reaction with sodium hydrosulphide gave the thione (100), presumably by the same mechanism although attack by the sulphur anion upon the methyl group followed by the loss of thione is possible.



(99) (100)

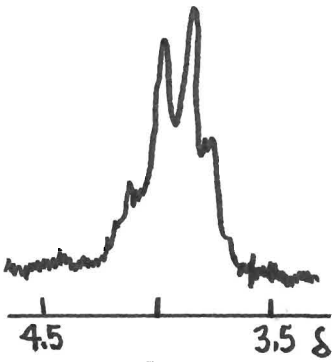
The salt (99) was then reacted with a variety of active methylene compounds under basic conditions; the results are listed in Table 9.

TABLE 9

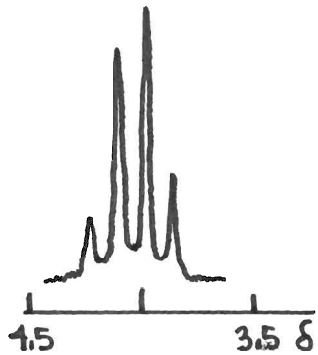


			Yield
$R_1=R_2=COEt$	(219)	$R_1=R_2=COEt$	54%
$R_1=R_2=COCH_3$	(126)	$R_1=H, R_2=COCH_3$	47%
$R_1=COEt, R_2=COCH_3$	(220)	$R_1=H, R_2=COEt$	22%
	(221)	$R_1=COCH_3, R_2=COEt$	29%

FIGURE 6

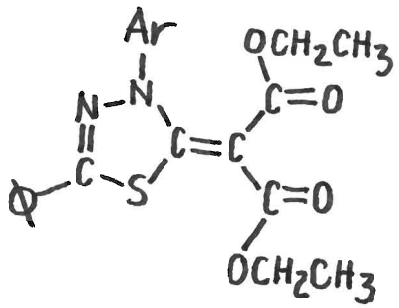


R.T.



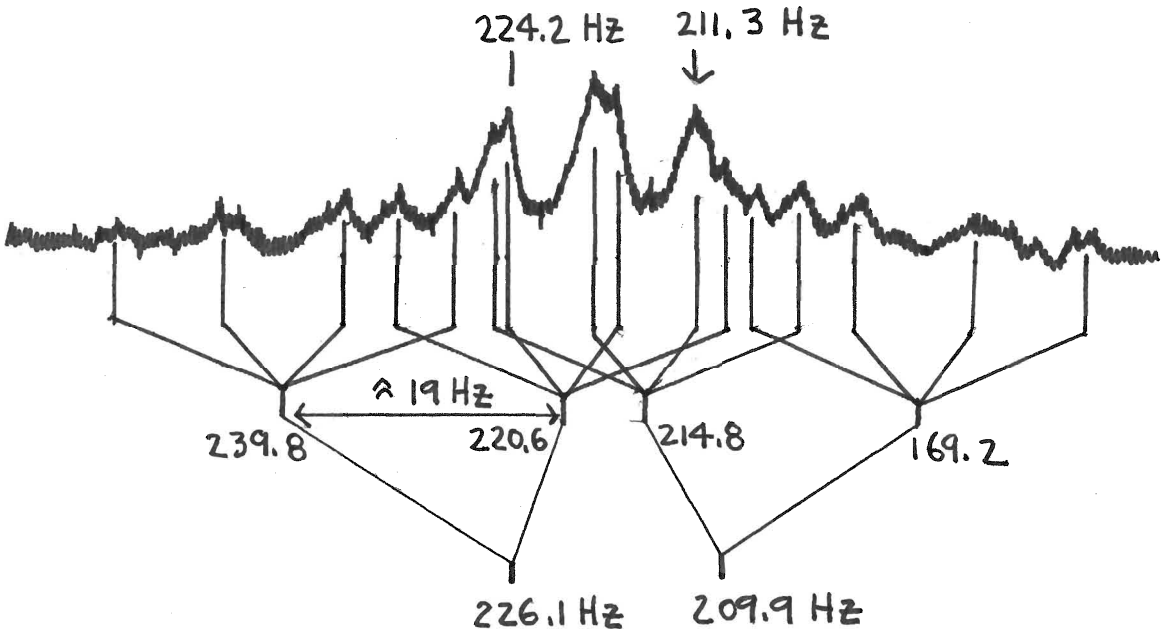
50°C

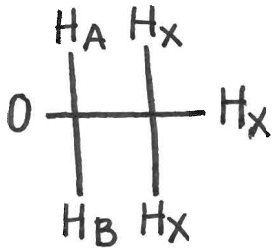
Methylene protons of



(219)

FIGURE 7





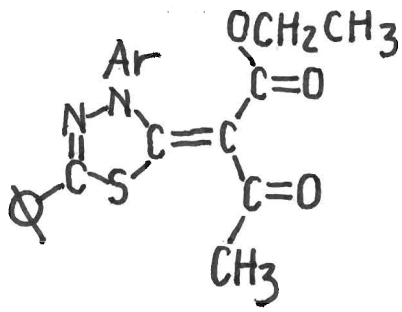
$J_{AX} = J_{BX} \approx 8$ Hz

$J_{AB} \approx 19$ Hz

$\nu_A = 226$ Hz

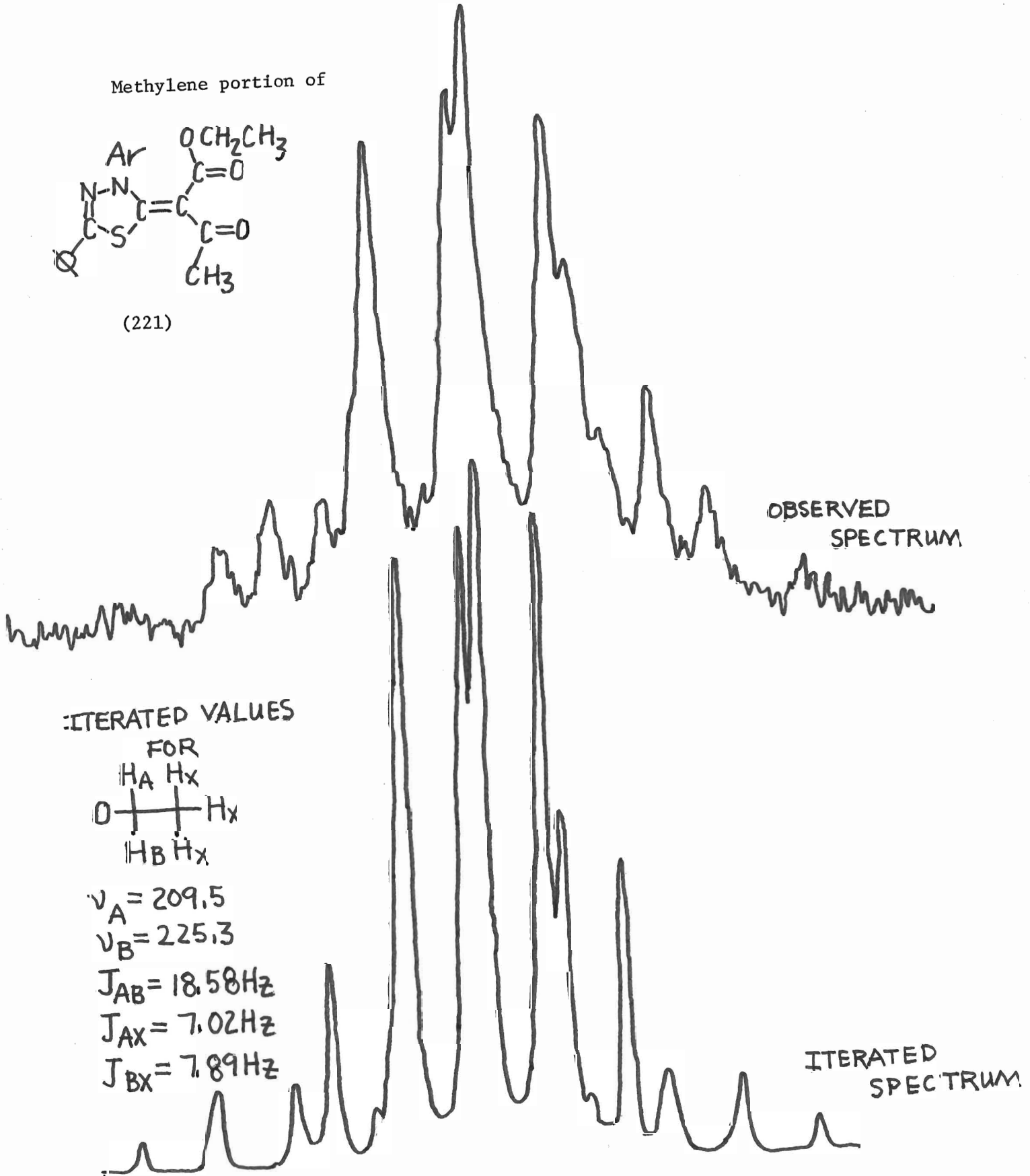
$\nu_B = 210$ Hz

Methylene portion of the p.m.r. spectrum of



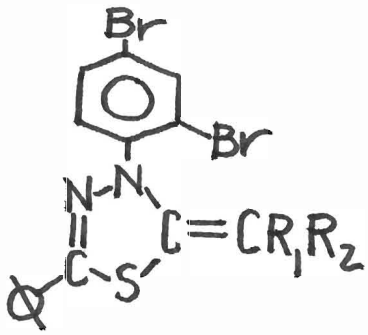
(221)

FIGURE 8


Methylene portion of
Ar
OCH2CH3
C=O
N-N
C=C
C=O
C-S
CH3
(221)
OBSERVED SPECTRUM
ITERATED VALUES FOR
HA Hx
Hx
HB Hx
νA = 209.5
νB = 225.3
JAB = 18.58Hz
JAX = 7.02Hz
JBX = 7.89Hz
ITERATED SPECTRUM

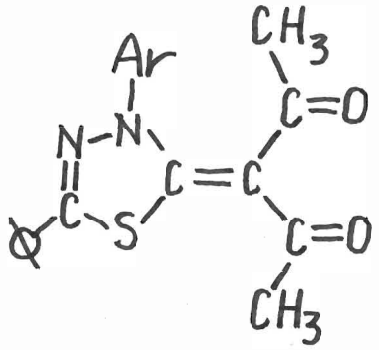
The compounds all gave satisfactory elemental analyses and the appropriate parent ions along with reasonable fragmentation patterns were observed in their mass spectra. The acetonylidene compound (126) was found to be identical with that already prepared. The p.m.r. spectra of the diacyl derivatives, (219) and (221) showed somewhat more complex splitting than would be expected for the methylene protons of the ethyl ester function. The methylene portion of the diethyl ester (219) is shown in figure 6 along with that of the methylene quartet observed for these protons when the temperature was raised to 50°C. For the acetyl ester (221) the ethyl portion appeared as an ABX_3 spin system and the methylene portion is shown in figure 7. This was analyzed in the same way as the ethyl portion of the ethyl ether (101) and the computer simulation is shown in figure 8. Decoupling the methyl protons caused the methylene multiplet to collapse to a broadened AB quartet.

The carbonyl stretches observed in the infrared spectra of these compounds are listed below.

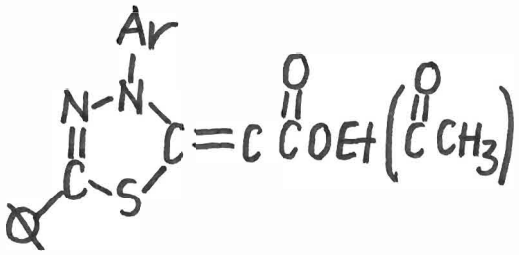


	ν(C=O) cm^{-1}
(219) $R_1 = R_2 = COEt$	1725, 1650
(220) $R_1 = H$, $R_2 = COEt$	1655
(221) $R_1 = CCH_3$, $R_2 = COEt$	1710, 1605
(126) $R_1 = H$, $R_2 = CCH_3$	1615

The unusual feature of this series of reactions is the apparent facile deacetylation of those compounds, (222) and (223), which were the expected products. A tentative mechanism would involve the

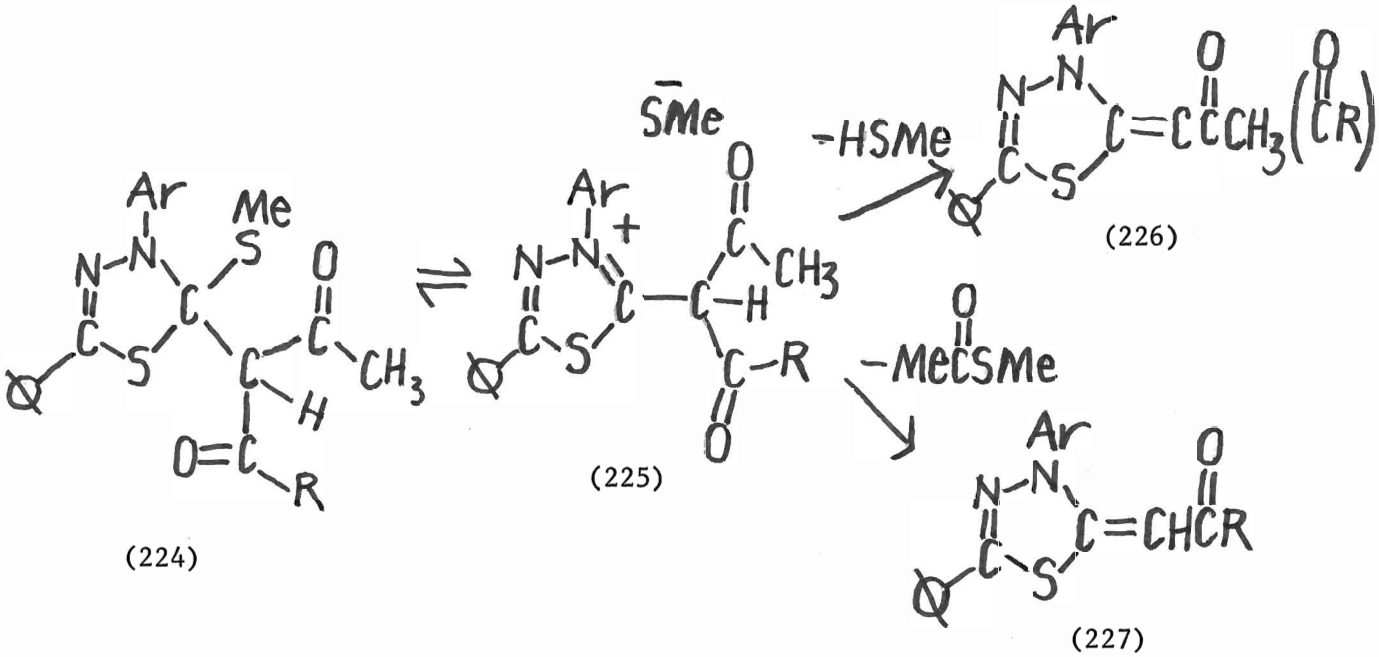


(222)



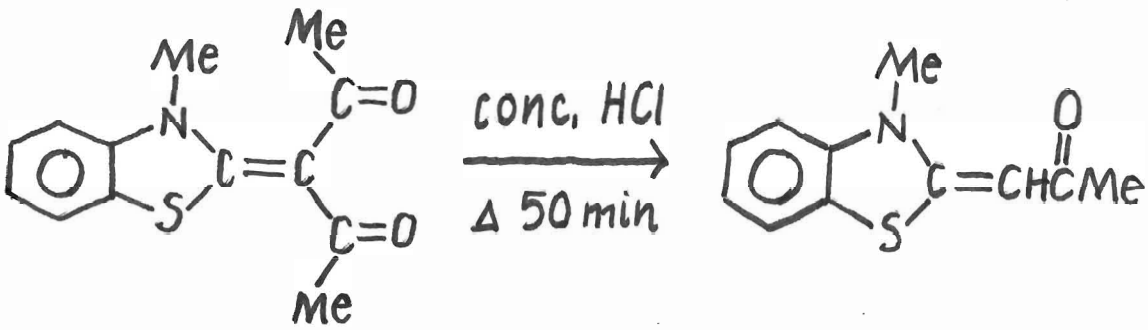
(223)

initially formed intermediate (224) undergoing the loss of the methyl mercapto anion to give (225). The methyl mercapto anion could then



(224) (225) (226) (227)

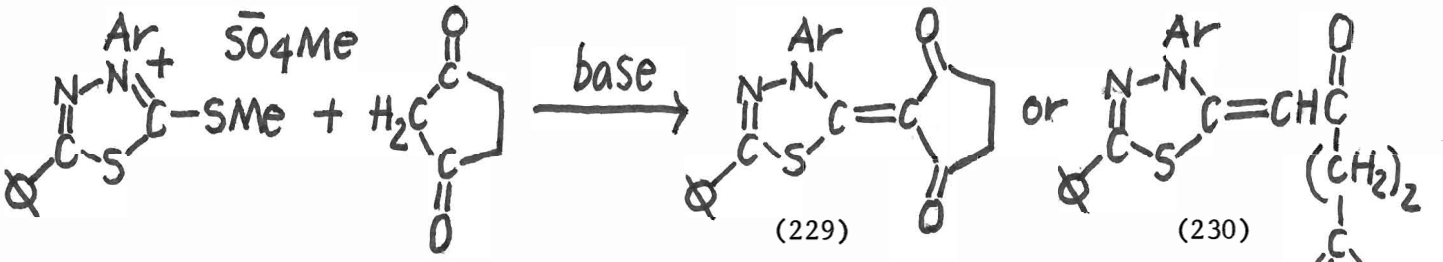
attack the acetyl group or abstract a proton to give (226) or (227). As well, once (226) has been formed, it could be deacetylated in the reaction medium. The closest analogue found was the deacetylation[76] of (228) but this was conducted under strongly acidic conditions.



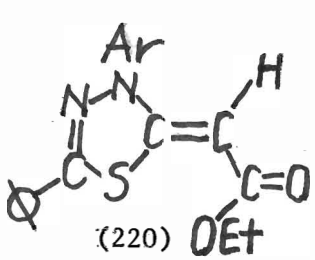
(228)

Some further insight into this reaction could be obtained by repeating the experiments with cyclic β-diketones where one would expect (229) or (230) or a mixture of the two as products. The apparent stability of the diester (219) under these conditions could be attributed to the greater electrophilic character of an acetyl group relative to that of an ester[10].

It was originally thought that the different carbonyl stretches in the infrared spectra of the diacyl anhydrobases and the apparent lack of rotational isomerism about the exocyclic carbon-carbon double bond would allow some insight into the preferred configuration of these molecules. That is, since the carbonyl absorption of (220) corresponds

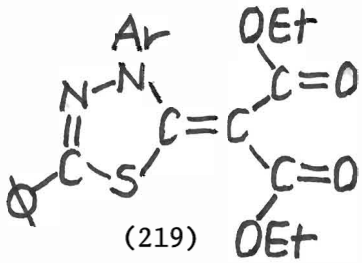


(229) (230)



(220)

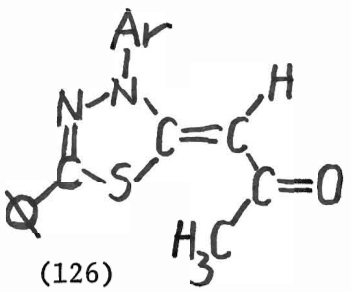
ν C=O, 1655 cm^{-1}



(219)

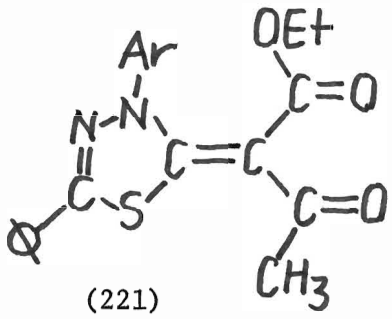
ν C=O, 1725 cm^{-1}, 1650 cm^{-1}

to the lower of the absorptions in the diester (219), it is tempting to suggest that conjugation with nitrogen is only possible for the carbonyl group trans to the nitrogen. The cis carbonyl group, because of a steric interaction with the N-aryl group, is kept out of the plane of the heterocyclic ring. A similar effect could then be used to explain the spectra of the acetyl-ester (221) where the lower frequency corresponds with that of the acetylated anhydrobase (126). The ABX_3



(126)

ν C=O, 1615 cm^{-1}



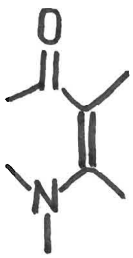
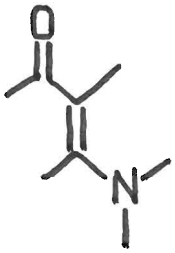
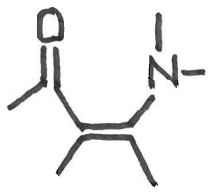
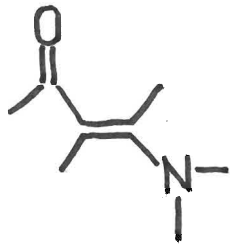
(221)

νC=O, 1710 cm^{-1}, 1605 cm^{-1}

multiplet observed for the ethyl group could then result from restricted rotation brought about by the interaction of this group with the N-aryl substituent.

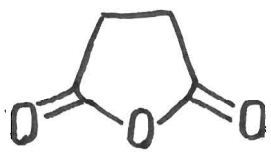
However, it is extremely doubtful if one could make a meaningful comparison between the carbonyl stretches in the two compounds. This is because there is probably a good degree of vibrational coupling between the exocyclic C=C and the C=O bonds in the monoacyl derivatives and the exocyclic C=C and the two C=O bonds in the diacyl derivatives. Taylor and coworkers[77,78], who are presently studying the effects of conformation and substitution upon the C=C and C=O stretching modes in α,β-unsaturated ketones, have published[78] the data contained in Table 10 to illustrate the conformational effects upon the stretching frequencies in ideal enamino-ketones.

TABLE 10

s-trans		s-cis		
				
1615	1595	1640	1620	νC=O
1585	1550	1565	1530	νC=C

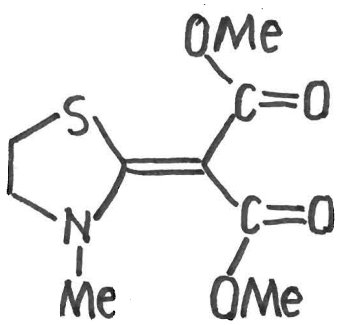
The differences observed in this series were thought to be due to the different degree of vibrational coupling brought about by the orientation of the two groups with respect to each other.

For 1,3-diketo systems there is a similar possibility of vibrational coupling. It has been frequently demonstrated[79] that such systems containing two identical carbonyl groups which would be expected to absorb at the same frequency, show two bands on either side of the expected mean. Some examples of this could include (231)[79] and (232)[80] although the origin of the splitting in the latter compound was not



ν C=O, 1875 and 1799 cm⁻¹

(231)

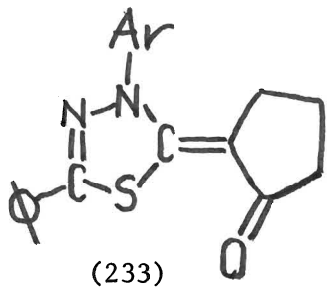


(232)

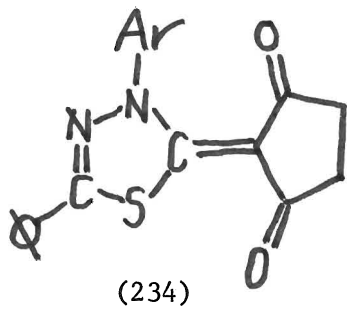
ν C=O, 1719 and 1692 cm⁻¹

mentioned.

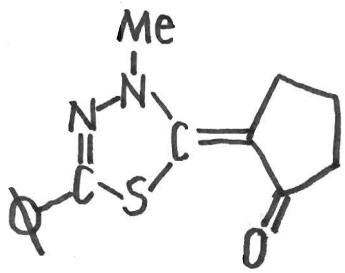
It can therefore be seen that the possibility of vibrational coupling in this system makes a comparison on the basis of the carbonyl stretching frequencies impossible. One would, in a similar fashion to Taylor and coworkers, have to make a detailed study of this system, examining all the possible isomers. This would involve the synthesis of compounds like (233), (234), (235) and (236) where the conformational possibilities are reduced and some idea of the steric effect could be obtained.



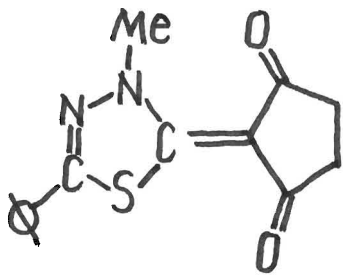
(233)



(234)

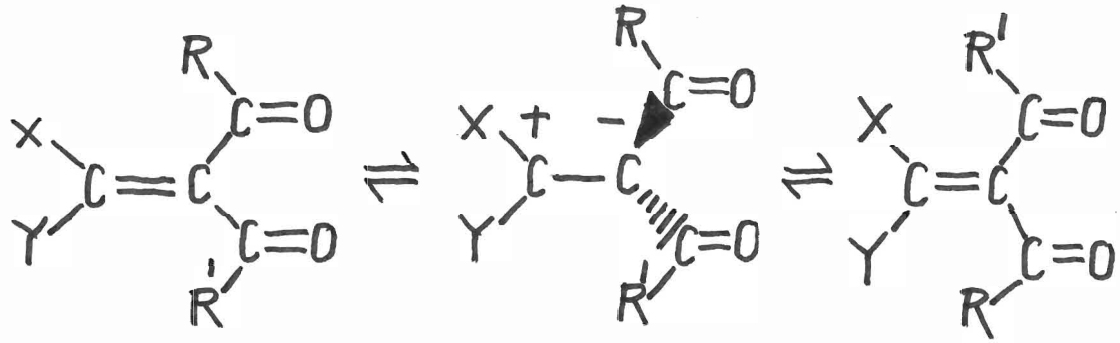


(235)



(236)

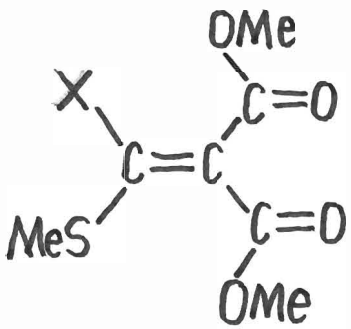
The p.m.r. data were similarly unusual when compared with results obtained for related systems. Rotation about the double bond in a diketo compound like (237) would involve the formation of a transition state such as (238). The energy barrier associated with this rotation



(237) (238)

would be lowered if the groups X and Y were capable of stabilizing the adjacent positive charge. The effects of different heteroatoms in the X and Y positions was studied by Shuo and Belsky[80] and the relevent aspects of their work are shown in Table 11.

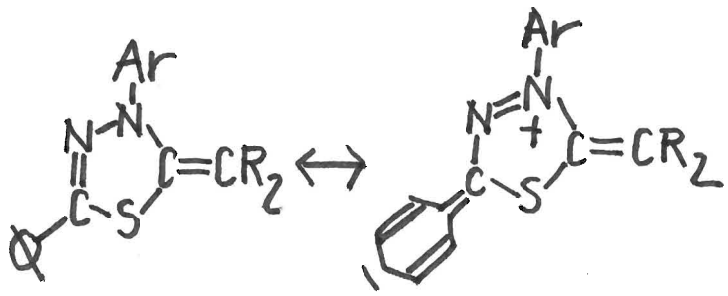
TABLE 11



X	temperature at which the p.m.r. OMe signals coalesced
Me	>200°
NMe_2	<-95°
NMeϕ	<-95°
	-72°

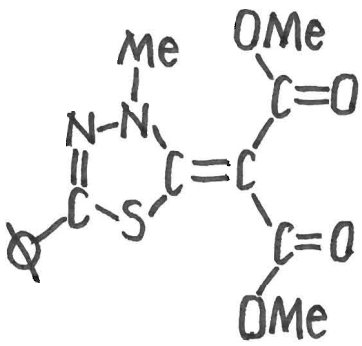
As can be seen, the introduction of nitrogen considerably reduces the energy barrier towards rotation about the C=C bond and in fact it was found necessary to introduce a p-nitrophenyl group (which was found to raise the energy barrier in a previous study) to make the rotation observable on a p.m.r. time scale.

It is therefore unusual that restricted rotation appears to be observed at room temperature when sulphur and nitrogen are incorporated in the thiadiazoline ring. Admittedly, the nitrogen is substituted with an aryl group and the thiadiazoline ring delocalizes some of its electron density (239) but the interaction between the N-aryl group and the acyl

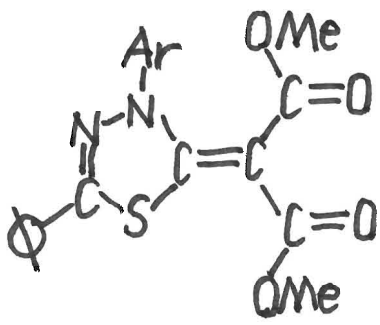


(239)

groups would be expected to raise the energy of the ground state[80]. This matter would require further study. Examining compounds such (240) and (241) would allow for comparison with the work of Shuo and Belsky.

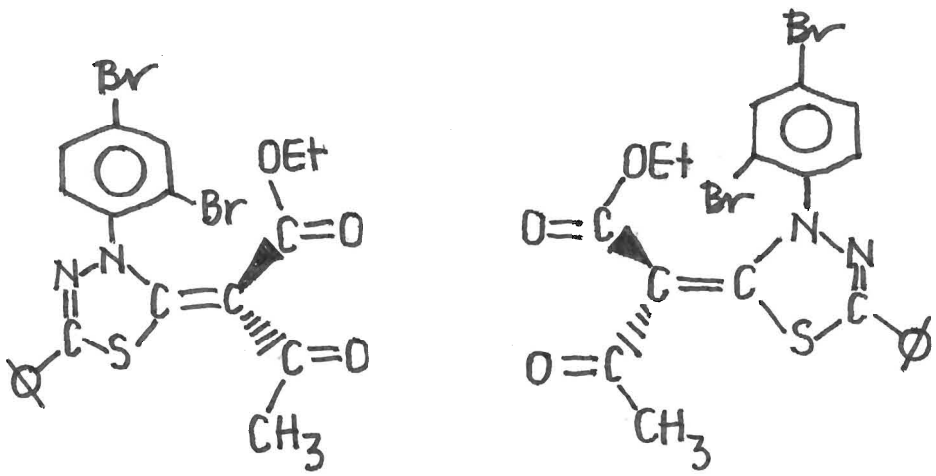


(240)



(241)

It is also noted that the p.m.r. spectra could be explained in terms of a steric effect similar to that observed in biphenyl compounds[81]. Assuming that the energy barrier for rotation about the C=C bond is sufficiently low but that there is a strong steric interaction between the 3-aryl group and the acyl group, then one would have the possibility of an object-image relationship for (221) where the acetoacetate portion of the molecule is kept from being in the plane of the thiadiazoline ring. The methylene portion of the ethyl ester would then be sensitive to the chiral center and hence the observed ABX_3 pattern.

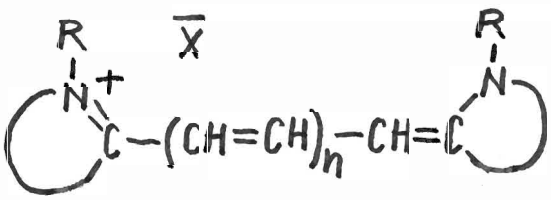


(221)

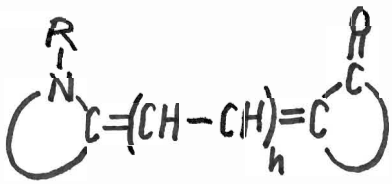
"CYANINE" TYPE DYES INCORPORATING THE 1,3,4-THIADIAZOLE RING

Cyanine and related dyes[82] possess one or more nitrogen containing heterocyclic rings united to the rest of the molecule by a double bond, a methine chain or an aza link (-N=). An enormous number of these dyes have been prepared and they cover the whole of the visible spectrum. However, because of their poor stability to light, they have not been used as textile dyes. The interest in these compounds stems from their unique efficiency as optical sensitizers. A normal photographic silver bromide emulsion is only sensitive to blue light of wavelength 350-450 nm . However, in 1873, H.W. Vogel found that the sensitivity of such an emulsion, when dyed with a cyanine dye, was extended to longer wavelengths. Since then thousands of these dyes have been prepared allowing for optical sensitization to green, red and even infrared. As a result, faster films capable of producing improved black and white photographs of coloured objects, aerial photography and colour photography were made possible.

In this discussion, only the cyanine (240) and merocyanine (241) dyes will be considered. The general synthetic methods for the preparation of these dyes have been outlined by Brooker[76] and Anderson[82].

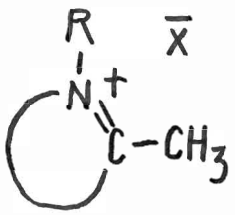


(240)

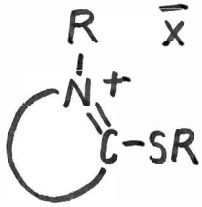


(241)

The common feature of these methods would be that they generally employ salts of the type (242) and (243).



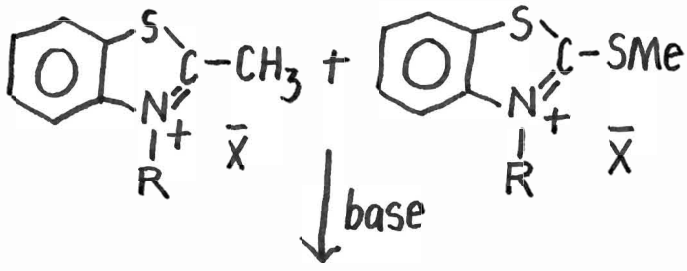
(242)

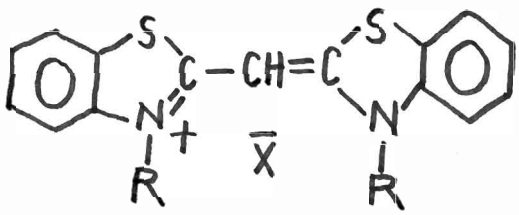


(243)

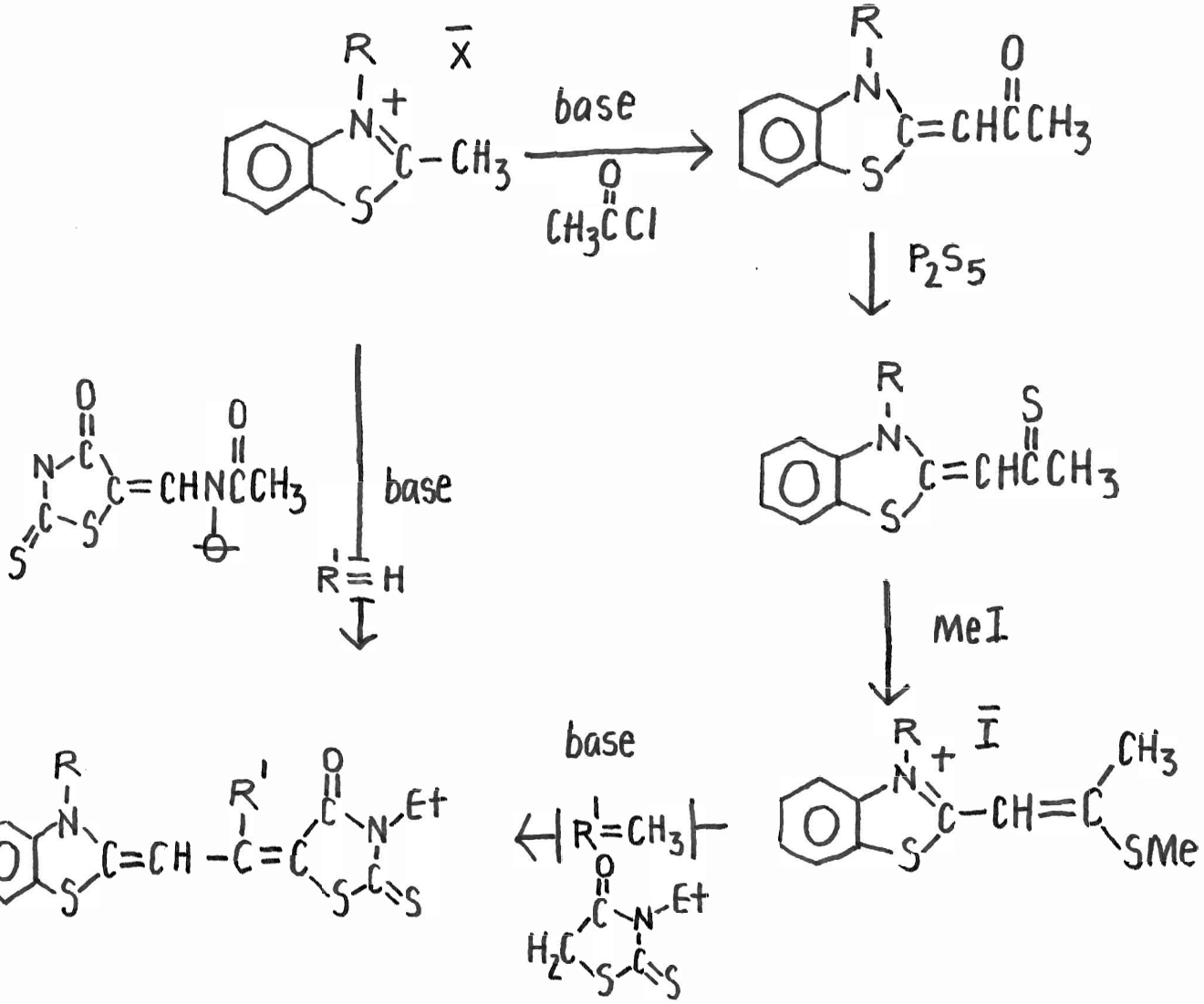
Some representative methods for the preparation of symmetrical cyanine dyes incorporating the 1,3-benzothiazole ring system would include:

(a) n = 0

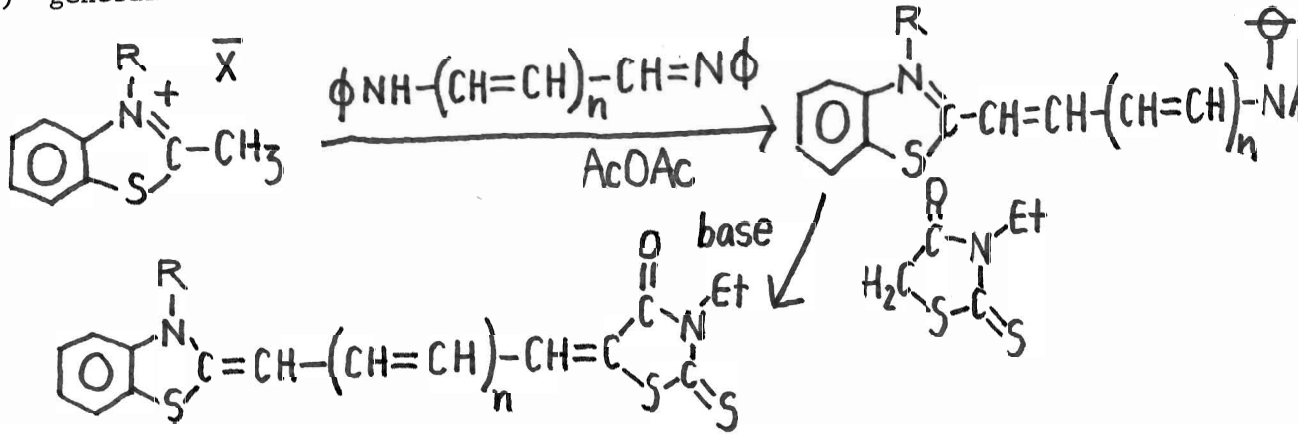




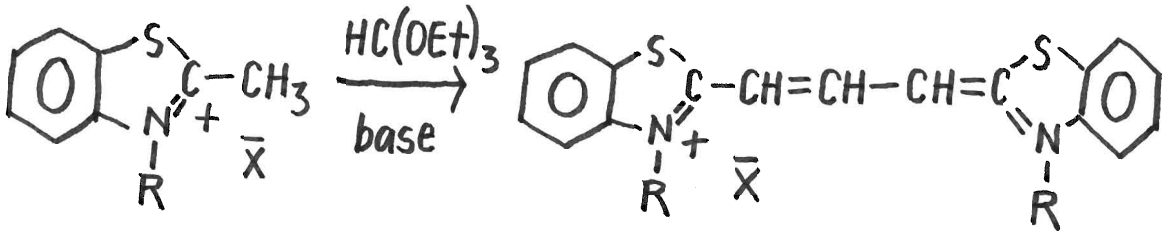
(b) n = 1



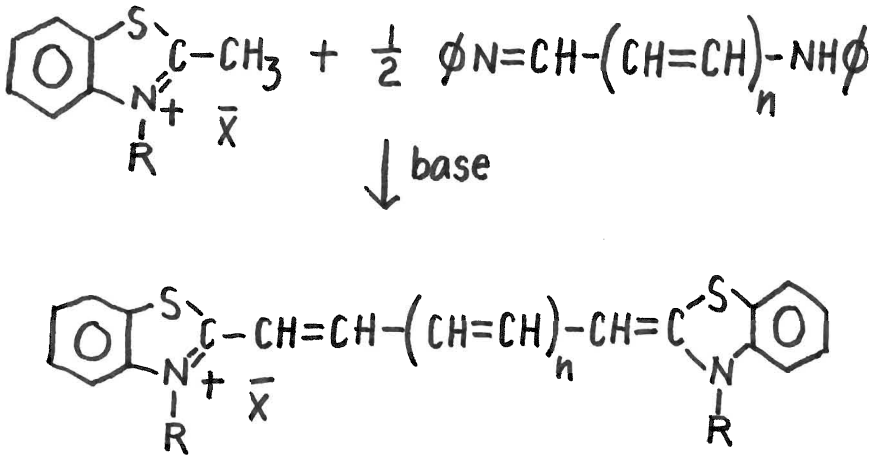
(c) general



(b) n = 1

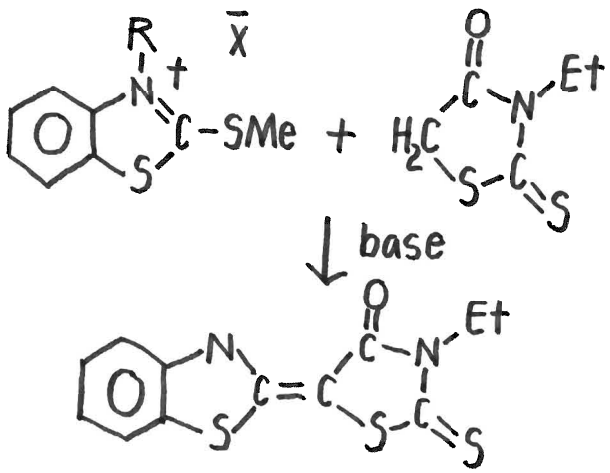


(c) general

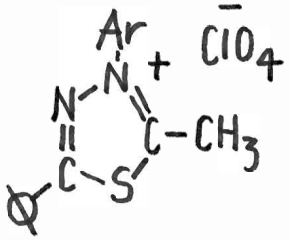


Considering the merocyanine dyes, some representative preparations[82,76] containing the 1,3-benzothiazole and 3-ethylrhodanine ring systems would include:

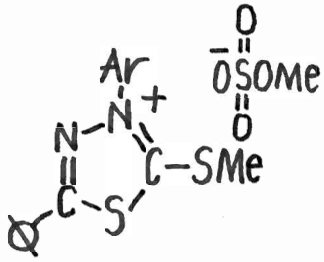
(a) n = 0



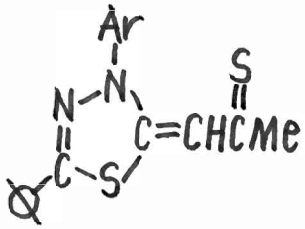
As mentioned in the introduction, merocyanine and cyanine dyes have been prepared incorporating the thiadiazole ring. Since the necessary precursors, (82), (99), and (117) were at hand, it was decided to prepare some of these dyes. These would differ from those known in the nature of the 3 and 5 substituents on the thiadiazole ring.



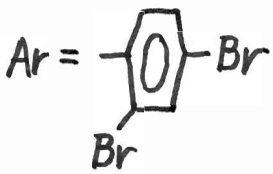
(82)



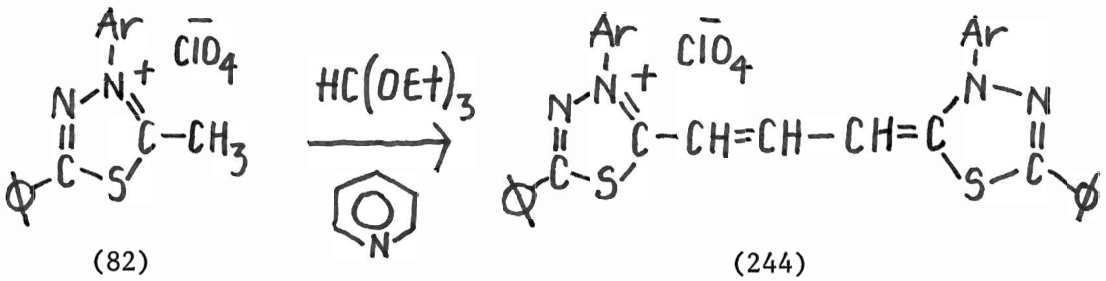
(99)



(117)



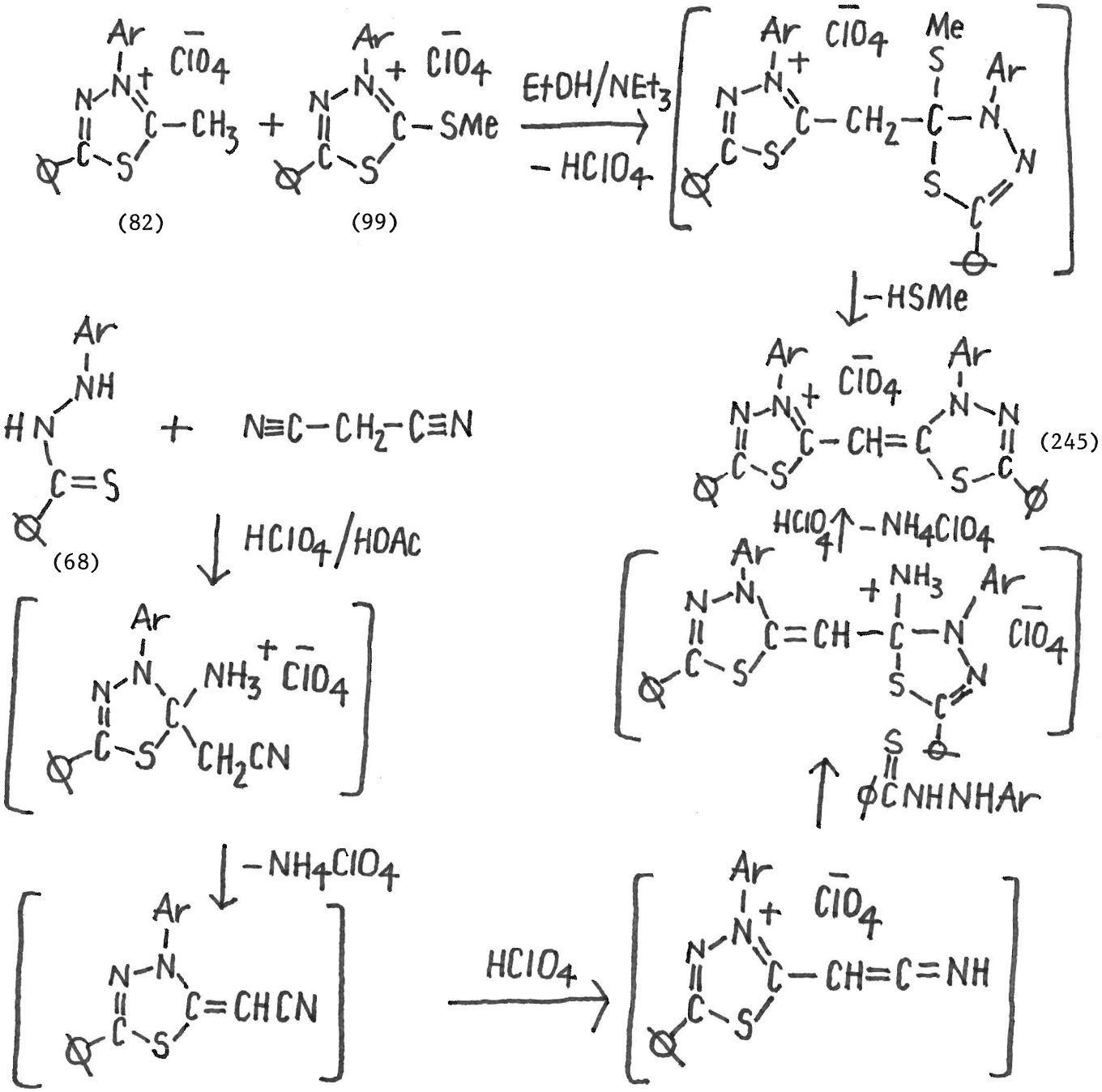
The cyanine dye (244) was prepared by refluxing the 2-methyl salt (82) with thiethylorthoformate in pyridine. The elemental analysis



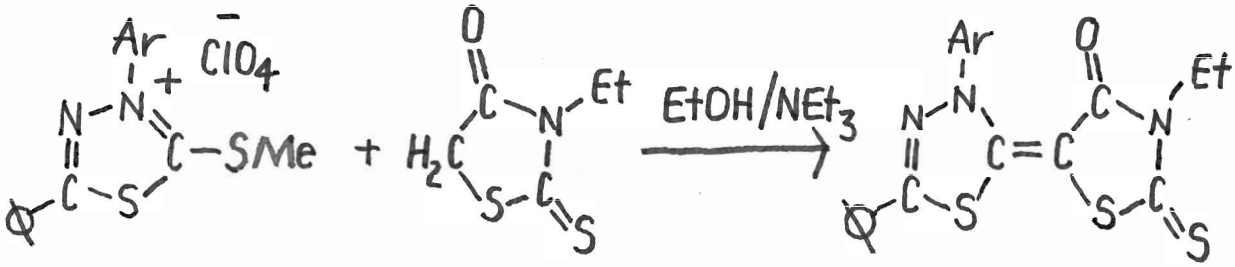
(82) (244)

for this compound indicated that one molecule of pyridine cocrystallized with two molecules of the dye. The presence of pyridine was confirmed by running a mass spectrum of this compound. Although a spectrum of the salt or a deprotonated species was not observed, that of pyridine was.

The monomethine cyanine dye (245) was prepared by refluxing the salts (82) and (99) in the presence of base and alternatively, by treating a suspension of the benzothiohydrazide (68) and malononitrile with perchloric acid. The dyes obtained by these different preparations were found to be identical in properties.

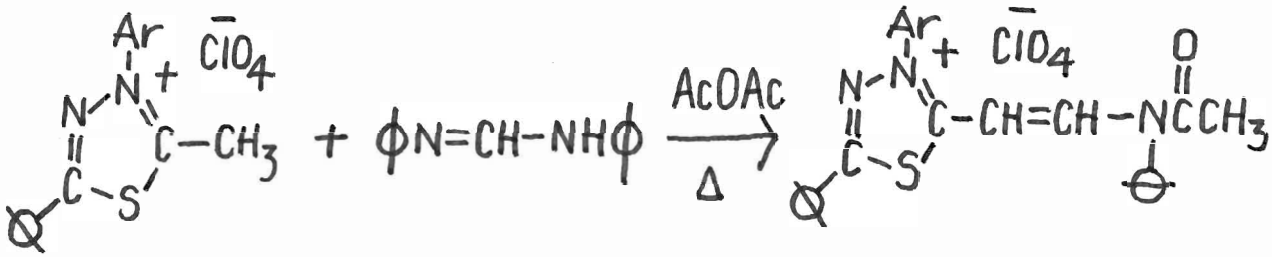


The lowest homologue (246) of the merocyanine series was prepared by reacting the salt (99) with 3-ethylrhodanine in the presence of base.



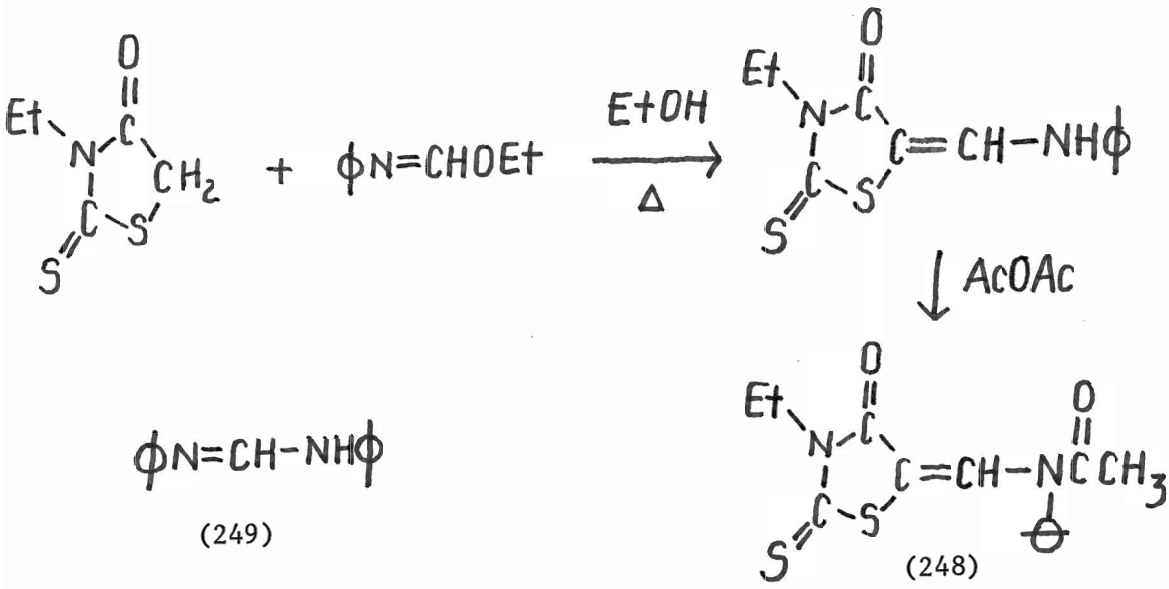
(99) (246)

An attempt was made to prepare the next higher homologue through the intermediate (247) according to the general method of Brooker and



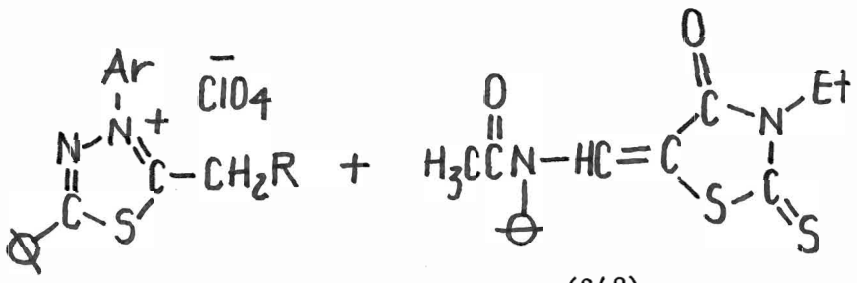
(82) (247)

coworkers[83]. This however, only gave a dark tar from which no product could be extracted. Therefore, an alternative approach was used. The intermediate (248) was prepared, but the method differed from that employed by Brooker and coworkers[84] who used (249) which required higher temperatures (kerosene, 120°C) and a longer heating period. This intermediate was then condensed with the 2-methyl (82) and the 2-ethyl (83) salts to give the merocyanine dyes (250) and (251).



(249)

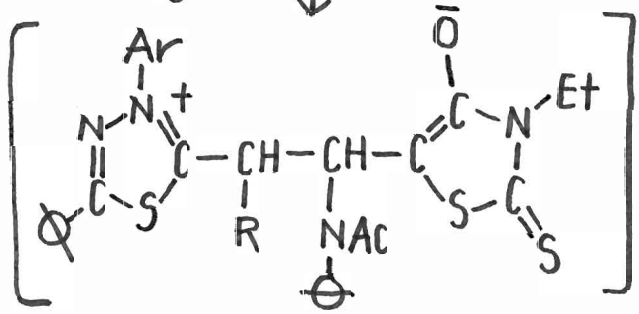
(248)

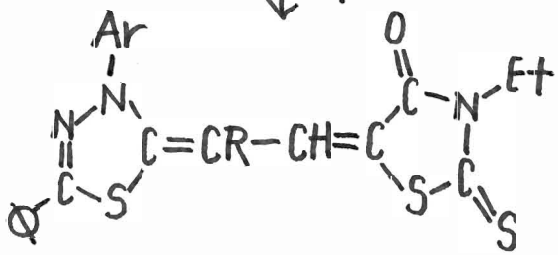


(248)

(82) R=H

(83) R=CH$_3$

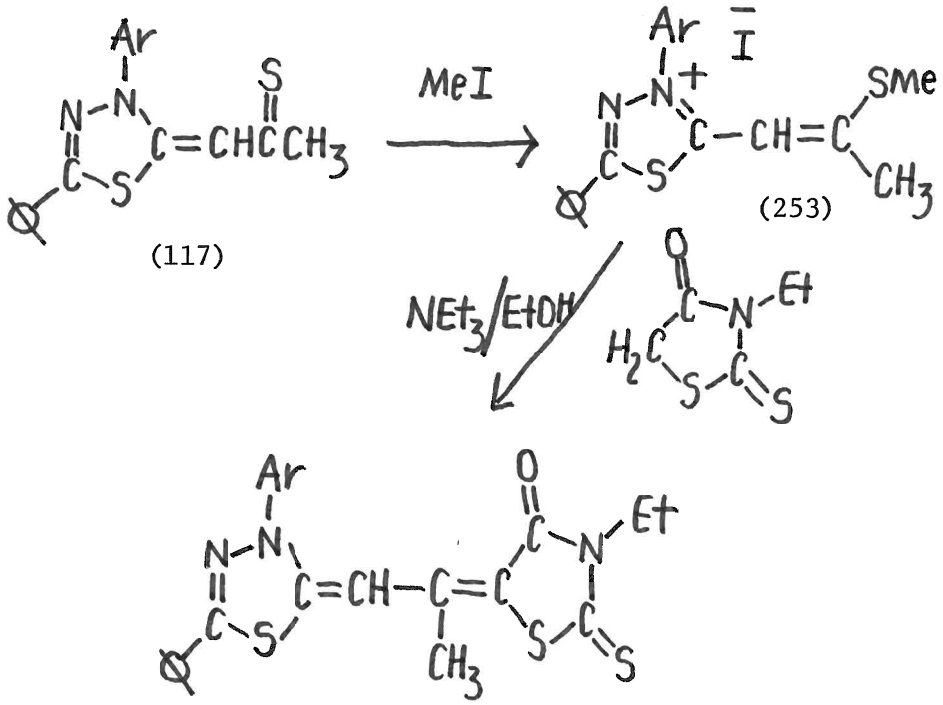




(250) R=H

(251) R=CH$_3$

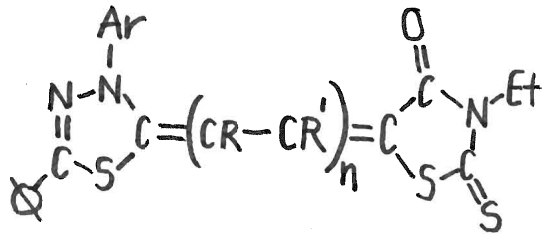
The other merocyanine dye (252) was prepared from the thioacetonylidene compound (117). This was methylated with methyl iodide but the resulting salt (253) was found to be relatively unstable, partial demethylation occurring when recrystallization was attempted. This was similarly observed[51] for the methiodides of the thioacetophenone compounds (140). It was condensed directly with 3-ethylrhodanine in the presence of base to give the dye (252).



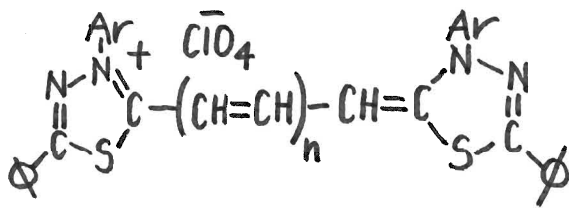
(252)

The yields along with the absorption maxima are recorded in Table 12. Satisfactory elemental analyses were obtained for all compounds prepared. The mass spectra of the merocyanine dyes all showed molecular ions and reasonable fragmentation patterns.

TABLE 12



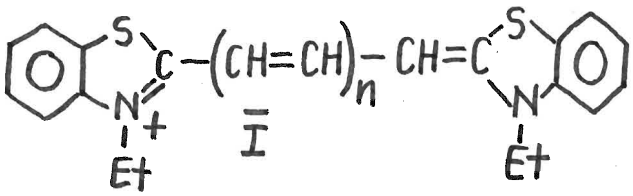
		yield	λ_{max}(EtOH) (nm)	log ε
(246)	n = 0	75%	424	4.70
(250)	n = 1 (R = R' = H)	83%	517	4.79
(251)	n = 1 (R = CH_3, R' = H)	55%	519	4.74
(252)	n = 1 (R = H, R' = CH_3)	83%	510	4.65



(245)	n = 0	77%	427	4.70
(244)	n = 1	81%	560	5.01

The colour of these dyes is determined by the length of the methine chain joining the two heterocyclic rings and the nature of the latter. In general, the λ_{max} indicates the energy difference between the ground and excited states of a molecule. A conjugated system of π electrons is stabilized by resonance and the stabilization is apparently greater in the excited state than the ground state since the addition of increasing numbers of double bonds in conjugation raises the wavelength of the

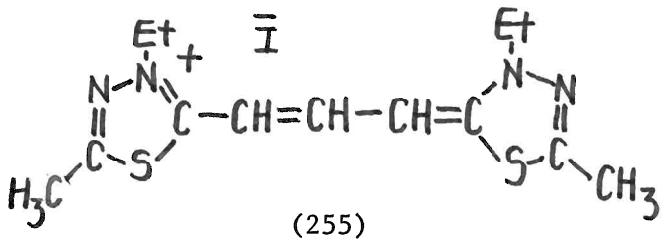
absorption maxima. In symmetrical cyanine dyes, the bathochromic shift[82] is approximately 100 nm for each additional bond. This is shown below for the benzothiazole cyanine dye series (254). It can be seen that the first two members of the thiadiazole series, (245) and



(254)

n	λ_{max} (nm)
0	422
1	557
2	650
3	762

(244) conform to this observation. The cyanine dye (255) has been prepared by Brooker and coworkers[17] and was found to have an absorption maximum at 514 nm (ethanol). This corresponds to a bathochromic shift of approximately 40 nm upon substituting aryl groups for alkyl groups



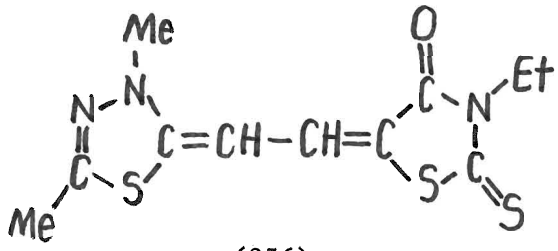
(255)

in the 3 and 5 positions of the thiadiazole rings.

Brooker,[85] who studied the effects of varying the nature of the substituents on a ring upon the absorption maxima, noted that an increase in the "basicity" or relative avidity with which a nuclei attracts a positive charge brings about a bathochromic shift. This was found by comparing a wide variety of symmetrical cyanine dyes incorporating

different ring systems. The other factor affecting the absorption maximum is the possibility of extra-chromophoric conjugation. Extended delocalization of the positive charge can bring about a bathochromic shift. This presumably accounts for the difference in the absorption maxima between (255) and (244).

The merocyanine dye (256) has also been prepared[16] and was found to have an absorption maximum at 560 nm (methanol). This corresponds to a bathochromic shift of approximately 40 nm relative to the analogous dye (250). In this instance, it appears that the substitution of aryl



(256)

groups for the methylthio and the methyl group brings about a reversal of the aforementioned effect and causes a shift towards lower wavelength.

Another factor which influences the absorption maxima is the effect of substituents on the polymethine chain which can bring about deviations from planarity. There are some slight differences between the merocyanine dyes (250), (251) and (252) but they are not large enough to make generalizations.

E X P E R I M E N T A L

Instrumentation and Techniques

Solvents

When necessary, solvents were dried according to procedures outlined in the Chemist's Companion[86].

Thin Layer Chromatography

This was carried out on "Baker-flex IB2-F" precoated silica gel slides. Chloroform was used for elution and visualization was effected by ultra-violet light or exposure to iodine vapour.

Column Chromatography

Unless otherwise stated, all columns were packed with silica gel (60-200 mesh).

Melting Points

Melting points were carried out on a Kofler hot stage microscope and the values quoted are uncorrected.

Elemental Analyses

Microanalyses were carried out by Dr. F. Pascher, Microanalytisches Laboratorium, Buschstrasse 54, Bonn, Germany.

Spectroscopic Data

The proton magnetic resonance (pmr) spectra were recorded on a "Varian A60" or a "Bruker WP60 FT" nuclear magnetic resonance spectrometer. Unless otherwise stated, they were obtained at ambient temperature, deuterochloroform being used as the solvent and tetramethylsilane as the internal standard. The chemical shifts are quoted in δ units and the splitting pattern identified as being a singlet (s), doublet (d), triplet (t), quartet (q) or a multiplet (m).

The infra-red spectra (ν_{max}) were recorded on a "Perkin-Elmer (model 377B)" or a "Perkin-Elmer (model 735)" grating infrared spectrophotometer. The compounds were mixed with potassium bromide and pressed into thin discs. The results are recorded (cm^{-1}) for the eight most important or intense peaks.

The mass spectral data (m/e) was obtained on an A.E.I. MS30, double beam, double focusing mass spectrometer. The results are tabulated as m/e values for the lowest isotopic species except in the case when the species contained one or two bromines. In this instance the m/e values for the respective doublets or triplets are recorded. This is followed by the relative intensities of the peak(s), a possible origin or an elemental formula and the corresponding metastable peak (m*) if observed. The molecular ion is referred to as M^{+}. Only the first eight peaks or the first seven plus the base peak are quoted.

The visible spectra (λ_{max}) were recorded on a "Hitachi-Perkin-Elmer (Coleman 124 model)" double beam grating spectrophotometer. The spectra were run using ethanol as the solvent and the absorption maximum quoted (nm) is followed by the logarithm of the extinction coefficient.

SECTION 1

Preparation of N'-Acyl-N'-aryl-benzothiohydrazides

(a) Acetyl chloride (1.7 ml) was added slowly to a solution of N'-(2,4-dibromophenyl)-benzothiohydrazide (68) (8.0 g) in dry pyridine (50 ml) at 0°. The resulting mixture was then stirred for 2h at room temperature after which it was poured into water (500 ml). Crystallization from ethanol afforded N'-acetyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (69) (7.0 g, 78%) as yellow prisms, m.p. 176-178° (lit.[25], 177-178°).

(b) Similarly, treatment of N'-phenyl-benzothiohydrazide (67) (2.3 g) in pyridine (20 ml) with acetyl chloride (0.8 ml) afforded N'-acetyl-N'-phenyl-benzothiohydrazide (72) (2.1 g, 78%), m.p. 147-150° (lit.[33], 154°) (benzene/hexane).

(c) Similarly, treatment of N'-(2,4-dibromophenyl)-benzothiohydrazide (68) (8.0 g) in pyridine (50 ml) with propionyl chloride (2.0 ml) afforded N'-(2,4-dibromophenyl)-N'-propionylbenzothiohydrazide (70) (8.6 g, 94%) as yellow prisms, m.p. 157-159° (ethanol) (Found: C, 43.76; H, 3.26; N, 6.31. $C_{16}H_{14}Br_2N_2OS$ requires C, 43.96; H, 3.16; N, 6.28%); ν_{max} 3200 (N-H), 1660 (C=O), 1460, 1390, 1330, 1300, 1240; pmr 1.0-1.5 (m, 3H, $-CH_2CH_3$), 2.0-3.0 (m, 2H, $-CO-CH_2CH_3$), 7.2-8.2 (m, 8H, arom.), 9.3 and 9.7 (d, 1H, -NH-); m/e 444/442/440 (<0.1%, M^+), 427/425/423 (7/11/7%, M^+-OH), 388/386/384 (1/2/1%, $M^+-C_3H_5O$)

363/361 (5/5%, M^+-Br), 345/343 (7/7%, 427/425/423-HBr, m* 279), 264 (14%, 345/343-Br, m* 203), 243/241/239 (16/30/18%), 78(100%, C_6H_5). (d) Benzoyl chloride (0.4 ml) was added to a stirred solution of N'-(2,4-dibromophenyl)-benzothiohydrazide (68) (1.0 g) in water (20 ml) containing a sodium hydroxide pellet. After being stirred for 30 min, a few drops of acetic acid were added to coagulate the colloidal suspension. The precipitate was collected, washed with water, and then dried. Crystallization from methylene chloride/hexane gave N'-benzoyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (71) (940 mg, 75%) as microscopic yellow needles, m.p. 127-129° (Found: C, 48.80; H, 3.04; N, 5.53. $C_{20}H_{14}Br_2N_2OS$ requires C, 49.00; H, 2.88; N, 5.72%); ν_{max} 3220 (N-H), 1665 (C=O), 1465, 1360, 1260, 1225, 690; pmr 7.2-8.2 (m, 13H, arom.), 10.0 (s, 1H, -NH-); m/e 492/490/488 (0.9/1.7/0.9%, M^+), 475/473/471 (0.1/0.3/0.1%, M^+-OH), 459/457/455 (0.9/1.8/0.9%, M^+-SH), 410/408 (7/6%, M^+-HBr), 371/369/367 (0.6/0.9/0.6%, M^+-C_6H_5CS), 357/355/353 (3/6/3%, M^+-C_6H_5CSN), 340/338/336 (1/2/1%, 475/473/471-C_6H_5CSN), 105 (100%, C_6H_5CO)

3-(2,3-Dibromophenyl)-2-(p-nitrobenzylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (80)

N'-(2,4-Dibromophenyl)-benzothiohydrazide (68) (1.0 g) and p-nitrophenylacetyl chloride (1.04 g) in dry benzene (10 ml) were heated at reflux for 30 min. After cooling, the precipitate was collected, washed with benzene, and dried (960 mg, 69%), m.p. 265-268°. Crystallization from pyridine/methanol afforded 3-(2,4-dibromophenyl)-2-(p-nitrobenzylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (80) as red prisms, m.p. 268-270° (Found: C, 47.54; H, 2.44; N, 7.79. $C_{21}H_{13}Br_2N_3O_2S$

requires C, 47.48; H, 2.47; N, 7.91%); ν_{max} 1585, 1560, 1540, 1475, 1325, 1310, 1200, 1110; m/e 533/531/529 (13/22/11%, M^+), 517/515/513 (0.8/1.1/0.8%, M^+-O), 503/501/499 (2.5/4.4/2.2, M^+-NO), 487/485/483 (0.9/1.8/0.7%, M^+-NO_2), 452/450 (25/21%, M^+-Br, m* 383), 406/404 (9/8%, 406/404-NO_2), 271 (78%, 452/450-Br, m* 305), 121 (100%, C_6H_5CS).

SECTION 2

Treatment of N'-Acyl-N'-2,4-dibromophenyl-benzothiohydrazides with Perchloric acid/Acetic anhydride

The general procedure of Boyd and Summers[4] was followed. The acyl benzothiohydrazide (1.0 g) was suspended in acetic anhydride (8 ml) and perchloric acid (0.8 ml) was added dropwise. If the product did not crystallize out of the reaction mixture, ether was added and the resulting gum was triturated with fresh ether until it solidified.

(a) N'-Acetyl-N'-2,4-dibromophenyl-benzothiohydrazide (69) under these conditions afforded 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.1 g, 88%), m.p. 173-174° (from acetic acid/ether) (Found: C, 35.40; H, 2.23; N, 5.33. $C_{15}H_{11}Br_2ClN_2O_4S$ requires C, 35.28; H, 2.16; N, 5.49%); ν_{max} 1510, 1460, 1440, 1380, 1090, 990, 850, 760; pmr (CD_3CN) 3.03 (s, 3H, CH_3), 7.4-8.3 (m, 8H, arom.); m/e 412/410/408 (salt-$HClO_4$).

(b) N'-(2,4-Dibromophenyl)-N'-propionyl-benzothiohydrazide (70) afforded 3-(2,4-dibromophenyl)-2-ethyl-5-phenyl-1,3,4-thiadiazolium perchlorate (83) (1.1 g, 94%), needles, m.p. 196-198° (from acetic acid/ether) (Found: C, 36.58; H, 2.52; N, 5.20%. $C_{16}H_{13}Br_2ClN_2O_4S$ requires C, 36.63; H, 2.50; N, 5.34%); ν_{max} 1630, 1510, 1480, 1460, 1440, 1090, 880, 850; pmr (CD_3CN) 1.57 (t, 3H, $-CH_3$), 3.2 (m, 2H, $-CH_2-$), 7.5-8.1 (m, 8H, arom.).

(c) N'-Benzoyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (71) afforded 3-(2,4-dibromophenyl)-2,5-diphenyl-1,3,4-thiadiazolium perchlorate (84) (1.0 g, 86%), prisms, m.p. 266-268° (from acetic acid) (Found: C, 41.70; H, 2.33; N, 4.86%. $C_{20}H_{13}Br_2ClN_2O_4S$ requires C, 41.94; H, 2.29; N, 4.89%); ν_{max} 1590, 1560, 1510, 1480, 1460, 1440, 1180, 1090.

Treatment of N'-2,4-Dibromophenylbenzothiohydrazide with Perchloric Acid/Acid Anhydrides

The procedure of Boyd and Summers[5] was again followed. The benzothiohydrazide (1.0 g) was suspended in the acid anhydride (8 ml) and perchloric acid (0.8 ml) was added dropwise. The product was separated as before.

(a) The benzothiohydrazide (69) with acetic anhydride afforded 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.14 g, 86%) m.p. and mixed m.p. 173-174° (from acetic acid/ether).

(b) The benzothiohydrazide (69) with propionic anhydride afforded 3-(2,4-dibromophenyl)-2-ethyl-5-phenyl-1,3,4-thiadiazolium perchlorate (83) (1.27 g, 94%), m.p. and mixed m.p. 196-198° (from acetic acid/ether).

Reaction of N'-Aryl-benzothiohydrazides with Nitriles in Perchloric Acid/Acetic Acid

The benzothiohydrazide (1 g) and the nitrile (1.2 equivalents) in acetic acid (2 ml) containing perchloric acid (1 ml) were heated at reflux for 5 min. The suspension was allowed to cool and water (20 ml) was slowly added with stirring. The white precipitate (ammonium perchlorate) dissolved and the thiadiazolium salt precipitated or oiled out.

(a) N'-(2,4-Dibromophenyl)-benzothiohydrazide (68) and acetonitrile afforded 3-(2,4-dibromophenyl-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g, 77%) m.p. and mixed m.p. 173-174° (from acetic acid/ether).

(b) N'-(2,4-Dibromophenyl)-benzothiohydrazide (68) and propionitrile afforded 3-(2,4-dibromophenyl)-2-ethyl-5-phenyl-1,3,4-thiadiazolium perchlorate (83) (1.2 g, 85%), m.p. and mixed m.p. 196-198° (from acetic acid/ether).

(c) N'-(2,4-Dibromophenyl)benzothiohydrazide (68) and benzonitrile afforded 3-(2,4-dibromophenyl)-2,5-diphenyl-1,3,4-thiadiazolium perchlorate (84) (1.1 g, 76%), m.p. and mixed m.p. 266-268° (from acetic acid).

(d) N'-Phenyl-benzothiohydrazide (67) and acetonitrile afforded 3,5-diphenyl-2-methyl-1,3,4-thiadiazolium perchlorate (94) (1.2 g, 77%), m.p. 149-153° (precipitated from acetic acid with ether) (Found: C, 51.02; H, 3.79; N, 7.70. $C_{15}H_{13}ClN_2O_4S$ requires C, 51.06; H, 3.71; N, 7.94%); ν_{max} 1600, 1525, 1500, 1460, 1340, 1100, 790, 700; pmr (CD_3CN) 2.96 (s, 3H, $-CH_3$), 7.5-8.1 (m, 10H, arom.); m/e 252 (salt-$HClO_4$).

(e) N'-Phenylbenzothiohydrazide (67) and benzonitrile afforded 2,3,5-triphenyl-1,3,4-thiadiazolium perchlorate (95) (1.1 g, 78%), prisms, m.p. 215-218° (lit.[6] 214-217°).

3-(2,4-Dibromophenyl)2-methylthio-5-phenyl-1,3,4-thiadiazolium Methosulfate (99)

3-(2,4-Dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazol-2-thione (100) (20 g) in dry benzene (50 ml) containing dimethylsulfate (13.6 g) was heated at reflux for 12 h. After standing in the refrigerator for

24 h, the white precipitate, which formed, was collected and washed with benzene. This gave 3-(2,4-dibromobenzene)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (24.8 g, 96%) as prisms, m.p. 200-205°. A sample crystallized from acetic acid/benzene had m.p. 208-210° (Found: C, 33.88; H, 2.35; N, 4.86. $C_{16}H_{14}Br_2N_2O_4S_3$ requires C, 34.67; H, 2.55; N, 4.86%); ν_{max} 1580, 1505, 1285, 1240, 1220, 1060, 1000, 760, 725; the mass spectrum was identical with that of 3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazol-2-thione (100).

To a solution of the methosulfate (99) (24 g) in acetic acid (500 ml) was added a solution of sodium perchlorate (75 g) in water (150 ml). The resulting suspension was stirred for 10 min and then a further 500 ml of water was added. The precipitate was collected and dried (20.3 g, 86%), m.p. 205-211°. A sample crystallized from acetic acid affording the perchlorate as prisms, m.p. 210-212° (Found: C, 33.24; H, 2.09, N, 5.26. $C_{15}H_{11}Br_2ClN_2O_4S$ requires C, 33.20; H, 2.04; N, 5.16%); ν_{max} 1590, 1560, 1510, 1480, 1410, 1370, 1290, 1100.

SECTION 3

2-Ethoxy-2,3,5-triphenyl-Δ^4-1,3,4-thiadiazoline (4)

2,3,5-Triphenyl-1,3,4-thiadiazolium perchlorate (95) (1.0 g) in dry ethanol (10 ml) containing triethylamine (0.67 ml) was heated at reflux for 15 min. The precipitate, obtained after allowing the solution to stand overnight, was collected and crystallized from ethanol. This gave 2-ethoxy-2,3,5-triphenyl-Δ^4-1,3,4-thiadiazoline (4) (540 mg, 63%) as prisms, m.p. 126-128 (lit.[3], 128.5-129.5°).

3-(2,4-Dibromophenyl)-2-ethoxy-2,5-diphenyl-Δ^4-1,3,4-thiadiazole (101)

(a) A suspension of 3-(2,4-dibromophenyl)-2,5-diphenylthiadiazolium perchlorate (84) (1.0 g) in dry ethanol (25 ml) containing triethylamine (0.6 ml) was heated at reflux for 30 min. The crystals which deposited upon cooling were collected and washed with ethanol. Crystallization from ethanol afforded 3-(2,4-dibromophenyl)-2-ethoxy-2,5-diphenyl-Δ^4-1,3,4-thiadiazoline (101) (810 mg, 79%) as prisms, m.p. 155-163° (Found: C, 50.72; H, 3.50; N, 5.19. $C_{22}H_{18}Br_2N_2OS$ requires C, 50.98; H, 3.50; N, 5.41%); ν_{max} 1475, 1445, 1330, 1225, 1065, 1750, 1685; pmr 1.37 (t, 3H, $\underline{CH_3}CH_2$-), 3.66 (m, 2H, -$\underline{CH_2}CH_3$), 7.11-7.85 (m, 13H, arom.); m/e 520/518/516 (1.4/2.4/1.4%, M^+), 475/473/471 (3.4/6.3/3.3%, $M^+-C_2H_5O$), 439/437 (5.9/5.4%, M^+-Br), 393/391 (1.4/1.1%), 371/369/367 (3.6/6.4/3.3%, $M^+-C_2H_4$+ C_6H_5CS), 354/352/350 (10/18.6/10%, 371/369/367-OH), 340/338/336 (1.3/2.1/1.3%, 354/352/350-N), 105 (100%, C_6H_5CO).

(b) Triethylamine (0.63 ml) was added to a solution of α-bromobenzaldehyde-2,4-dibromophenylhydrazone (65) (1.0 g) and ethyl thiobenzoate (770 mg) in dry benzene (25 ml). After stirring the suspension for 30 min, the precipitate was collected, washed with water and crystallized from ethanol. This afforded the thiadiazoline (101) (1.03, 87%) as prisms melting in the range 155-165° and having a pmr spectrum identical with that of the foregoing sample.

Reaction of 3-(2,4-Dibromophenyl)-2-ethoxy-2,5-diphenyl-Δ^4-1,3,4-thiadiazoline (101) with water

A solution of the thiadiazoline (101) (200 mg) in acetonitrile (20 ml) containing water (5 ml) was heated at reflux overnight. The solution was allowed to cool and further water was added. The precipitate was collected, dried, and crystallized from methylene chloride/hexane. This afforded N'-benzoyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (71) (140 mg, 74%), m.p. and mixed m.p. 127-129°.

3-(2,4-Dibromophenyl)-2-methyl-2-methoxy-5-phenyl-Δ^4-1,3,4-thiadiazoline (111)

To a solution of 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g) in a mixture of dry acetonitrile (25 ml) and dry methanol (25 ml) was added triethylamine (0.55 ml). After standing in the refrigerator for a day, the crystals which formed were collected, washed with dry methanol and dried in a vacuum desiccator. This gave 3-(2,4-dibromophenyl)-2-methyl-2-methoxy-5-phenyl-Δ^4-1,3,4-thiadiazoline (111) as pale orange prisms (640 mg, 80%), m.p. 115-120° (Found:

C, 43.66; H, 3.31; N, 6.32. $C_{16}H_{14}Br_2N_2OS$ requires C, 43.46; H, 3.19; N, 6.34%); ν_{max} 1475, 1375, 1345, 1110, 850, 825, 760, 685; pmr 1.91 (s, 3H, $-CH_3$), 2.31 (s, 3H, $-O-CH_3$), 7.2-7.8 (m, 8H, arom.); m/e 412/410/408 (23.1/41/8/21.3%, M-MeOH), 331/329 (43.8/43.8%, 412/410/408-Br), 250 (100%, 331/329-Br), 237/235/233 (5.0/10.0/5.0%, $C_6H_3Br_2$), 228/226 (12.5/11.3%, 331/329-C_6H_5CN), 201/202 (4.4/4.4%), 182/180 (10.6/9.4%, 228/226-SCH_2), 175 (8.6%, 250-C_6H_3).

Reaction of 3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) with Base

To a solution of the 2-methylthiadiazolium perchlorate (82) (1.0 g) in dry acetonitrile (15 ml) was added triethylamine (0.55 ml). After stirring for 30 min, the oil which initially deposited, solidified. This was collected, washed with water and dried. This afforded 3-(2,4-dibromophenyl)-2-[(3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazolin-2-ylidene)-methylene]-2-methyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (115) (650 mg, 81%) as a yellow solid, m.p. 157-160° (Found: C, 43.97; H, 2.63; N, 6.83. $C_{30}H_{20}Br_4N_4S_2$ requires C, 43.92; H, 2.47; N, 6.83%); ν_{max} 1600, 1470, 1380, 1270, 1210, 980, 765, 690; pmr 1.8 (s, 3H, $-CH_3$), 4.3 (s, 1H, =C-H), 7.2-8.0 (m, 16H, arom.); when a low probe temperature was used, the mass spectrum showed the peak at highest m/e corresponding to the monomeric species (112), 412/410/408.

Reaction of the Dimeric Compound (115) with Acid

A solution of 3-(2,4-dibromophenyl)-2-[(3-(2,4-dibromophenyl-5-phenyl-Δ^4-1,3,4-thiadiazolin-2-ylidene)-methylene]-2-methyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (115) (500 mg) in acetic acid (5 ml) containing perchloric acid (1 ml) was heated at reflux for 30 min. The solution was allowed to cool and then ether was added to the point of incipient turbidity. This deposited 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (380 mg, 61%), m.p. 171-173° and mixed m.p. 171-173°. The pmr. spectrum was identical with that already described.

Alternate Synthesis of the Dimer (115)

To a suspension of 3-(2,4-dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (117) (500 mg) and N-α-bromobenzylidene-N'-(2,4-dibromophenyl)-hydrazine (65) (460 mg) in dry acetonitrile (20 ml) was added triethylamine (0.5 ml). The suspension was stirred for 2h, after which the yellow solid was collected, washed with water and dried. This afforded the dimeric compound (115) as a yellow solid (720 mg, 82%), m.p. 149-154° and mixed m.p. 149-156°. The pmr spectrum was identical with that already described except for a small peak at δ 2.7 which was attributed to the presence of some of the unreacted thioacetonylidene compound. This was confirmed by t.l.c.

2-Acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126)

3-(2,4-Dibromophenyl)-2-methoxy-2-methyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (111) (500 mg) in acetic anhydride (5 ml) was heated at reflux for 30 min. The red solution was poured into water and the precipitate obtained upon stirring collected. Column chromatography using silica gel with benzene as eluant, followed by crystallization from acetonitrile afforded 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (301 mg, 59%) as tan coloured prisms, m.p. 155-157° (lit.[25], 155-156°); ν_{max} 1615 (C=O), 1530, 1495, 1480, 1470, 1440, 1170, 755; pmr 2.12 (s, 3H, CH_3-C=O), 5.45, (s, 1H, H-C=), 7.2-8.0 (m, 8H, arom.); m/e 454/452/450 (20/32/17%, M^+), 439/437/435 (6/11/6%, M^+-CH_3), 412/410/408 (3/5/3%, M^+-CH_2CO), 373/372 (100/92%, M^+-Br), 358/356 (77/68%, 373/371-CH_3), 331/329 (43/43%, 373/371-CH_2CO), 292 (6%, 373/371-CH_3), 250 (30%, 292-CH_2CO).

3-(2,4-Dibromophenyl)-2-(2,4-dinitrobenzylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (123)

3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g) and 2,4-dinitrofluorobenzene (1.0 g) in dry ethanol (20 ml) containing triethylamine (0.54 ml) were heated at reflux for 1 h. After cooling the precipitate was collected and crystallized from pyridine/methanol. This afforded 3-(2,4-dibromophenyl)-2-(2,4-dinitrobenzylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (123) (910 mg, 81%) as dark red prisms, m.p. 262-264° (Found: C, 43.98; H, 2.26;

N, 9.72%. $C_{21}H_{12}Br_2N_4O_4S$ requires C, 43.77; H, 2.10; N, 9.72%); ν_{max} 1580, 1545, 1520, 1500, 1460, 1320, 1280, 1125; m/e 578/576/574 (3.1/5.1/2.8%, M^+), 561/559/557 (4.1/6.2/3.6%, M^+-OH), 427/425/423 (4.1/6.2/3.6%, $M^+-C_6H_3NONO_2$), 414/412/410 (1.0/1.5/1.0%), 399/397/395 (2.8/5.4/2.7%, 427/425/423-COO, 377/375 (1.8/1.8%), 354/352/340 (2.6/4.9/2.6%, 299/297/295-SH), 103 (100%, C_6H_5CN).

3-(2,4-Dibromophenyl)-2-(p-dimethylaminostyryl)-5-phenyl-1,3,4-thiadiazolium perchlorate (124)

3-2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (500 mg) and p-dimethylaminobenzaldehyde (180 mg) in acetic anhydride (5 ml) were heated at reflux for 20 min. The precipitate was collected and crystallized from pyridine/methanol to give 3-(2,4-dibromophenyl)-2-(p-dimethylaminostyryl)-5-phenyl-1,3,4-thiadiazolium perchlorate (124) (510 mg, 81%) as green prisms, m.p. 263-265° (Found: C, 45.09; H, 3.03; N, 6.38. $C_{24}H_{20}Br_2ClN_3O_4S$ requires C, 44.91; H, 3.14; N, 6.55%); ν_{max} 1580, 1530, 1470, 1440, 1380, 1275, 1175, 1100; λ_{max} 555 (4.91).

Preparation of Several Acyl and Thioacyl Derivatives of the Anhydrobase (112)

(a) 2-Acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126)

3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.8 g) in acetic anhydride (10 ml) containing sodium acetate (320 mg) was heated at reflux for 30 min. The usual workup afforded the thiadiazoline (126) (1.21, 76%) as tan coloured prisms, m.p. 149-154°. Successive recrystallizations gave material of m.p. and mixed m.p. 155-157°.

(b) 2-(2-Butanon-1-ylidene)-3-(3,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (127)

3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g) in propionic anhydride (5 ml) containing a pellet of sodium hydroxide was heated at reflux for 30 min. The usual workup afforded 2-(2-butanon-1-ylidene)-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (127) (500 mg, 55%) as tan coloured needles (95% ethanol), m.p. 116-118° (Found: C, 46.47; H, 3.02; N, 6.01. $C_{18}H_{14}Br_2N_2OS$ requires C, 46.36; H, 3.03; N, 6.01%); ν_{max} 1600 (C=O), 1535, 1495, 1455, 1165, 825, 760, 685; pmr 1.13 (t, J = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2-), 2.41 (q, J = 7.2 Hz, 2H, -$\underline{CH_2}$-CH_3), 5.47 (s, 1H, H-C=), 7.2-8.0 (m, 8H, arom.); m/e 468/466/464 (19/32/19%, M^+), 439/437/435 (35/58/32, M^+-CH_3CH_2), 425/423/421 (1.2/2.3/1.6%, M^+-CH_3CO),

412/410/408 (2.3/4.2/2.6%, M^+-CH_3CHCO), 387/385 (39/35%, M^+-Br, m* 320), 358/356 (100/93%, 439/437/435-Br, m* 292), 306 (1.6%, 387/385-Br), 304/302/300 (3.6/6.1/3.2%, 439/437/435-C_6H_5CSN).

(c) 3-(2,4-Dibromophenyl)-5-phenyl-2-thioacetophenonylidene-Δ^4-1,3,4-thiadiazoline (128)

Triethylamine (0.8 ml) was added to a stirred suspension of 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.5 g) in dry ethanol (50 ml). After 5 min, thiobenzoylthioglycolic acid (3.1 g) was added and the suspension heated at reflux for 20 h. The solvent was removed and the red solid taken up in chloroform (100 ml). This was washed with 5% sodium hydroxide (2 x 100 ml), water (3 x 100 ml) and then dried (sodium sulfate). Removal of the chloroform followed by column chromatography on silica gel, using benzene as eluent, and crystallization from chloroform/light petroleum (30-60°) gave 3-(2,4-dibromophenyl)-5-phenyl-2-thioaceotphenonylidene-Δ^4-1,3,4-thiadiazoline (128) (1.0 g, 68%) as orange needles, m.p. 224-227° (Found: C, 48.80; H, 3.04; N, 5.53. $C_{22}H_{14}Br_2N_2S_2$ requires C, 49.00; H, 2.88; N, 5.72%); ν_{max} 1525, 1490, 1480, 1460, 1440, 1260, 860, 725; pmr 7.03 (s, 1H, H-C=), 7.26-8.03 (m, 13H, arom.); m/e 531/529/527 (2.9/4.4/2.5%, M^+-H), 451/449 (41.7/37.5%, M^+-Br, m* 389), 429/427/425 (13.5/25.0/11.9%, M^+-ϕCN), 419/417 (5.0/4.6%, 451/449-S), 370 (4.8%, 451/449-Br, m* 304), 364/362/360 (5.6/10.4/5.4%, 429/427/425-S_2H), 3.7/316 (11.5/13.1%, 419/417-$HC_2C_6H_5$), 102 (100%, $HC_2C_6H_5$).

(d) 2-Acetonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (129)

3,5-Diphenyl-2-methyl-1,3,4-thiadiazolium perchlorate (94) (1.0 g) was added to an ice-cooled suspension of dry pyridine (10 ml) containing acetyl chloride (0.26 ml). The suspension was stirred at room temperature until solution was attained (approximately 1 h). The solution was then poured into water (100 ml) and the precipitate obtained upon stirring was collected. Repeated crystallization from ethanol afforded 2-acetonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (129) (420 mg, 50%) as gray needles, m.p. 151-153° (lit.[26], 152-153°); ν_{max} 1600 (C=O), 1530, 1490, 1460, 1420, 1160, 760, 710, 680; pmr 2.17 (s, 3H, CH_3-), 6.01 (s, 1H, H-C=), 7.4-8.1 (m, 10H, arom.).

Mass spectrum (includes ions >2.0% and >m/e 100)

m/e	relative abundance	m/e	relative abundance
296	5.0%	216	m*
295	13.2%	176	3.2%
294	67.9%	149	2.5%
293	1.8%	148	8.2%
281	6.1%	145	3.6%
280	17.5%	144	35.7%
279	100.0%	132	2.5%
277	9.3%	121	8.2%
265	m*	116	5.7%
261	m*	109	9.6%
252	5.4%	104	8.9%
251	9.3%	103	11.1%

SECTION 4

Reactions of N'-Acyl-N'-aryl-benzothiohydrazides with Acid Anhydrides

(a) N'-Acetyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (69) (1.0 g) in acetic anhydride (10 ml) was heated at reflux for 1 h. The red solution was then poured into water and the precipitate obtained upon stirring collected. Column chromatography using silica gel with benzene as eluent, followed by crystallization from acetonitrile gave 2-acetonylidene-2-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (730 mg, 69%) as tan coloured prisms, m.p. and mixed m.p. 155-157°.

(b) N'-Acetyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (69) (1.0 g) in a mixture of propionic anhydride (3 ml) and acetonitrile (3 ml) was heated at reflux for 2 h. The usual workup followed by crystallization from 95% ethanol gave 2-(2-butanon-1-ylidene)-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (127) (690 mg, 63%) as tan coloured needles, m.p. and mixed m.p. 117-118°.

(c) N'-(2,4-dibromophenyl)-N'-propionylbenzothiohydrazide (70) (1.0 g) in acetic anhydride (10 ml) was heated at reflux for 1 h. The usual workup followed by crystallization from benzene/hexane afforded 2-(2-butanon-3-ylidene)-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-thiadiazoline (149) (790 mg, 74%) as pale yellow prisms, m.p. 169-172° (Found: C, 46.14; H, 2.99; N, 5.91. $C_{18}H_{14}Br_2N_2OS$ requires C, 46.36; H, 3.03; N, 6.01%); ν_{max} 1600 (C=O), 1455, 1430, 1325, 1120, 860, 760, 685; pmr 1.55 (s, 3H, CH_3-C=), 2.25 (s, 3H, CH_3C=O), 7.2-7.8 (m, 8H, arom.);

m/e 468/466/464 (62.100/59%, M^+), 453/451/449 (4/8/5%, M^+-CH_3), 425/423/421 (8/15/8%, $M^+-C_2H_3O$), 387/385 (100/100%, M^+-Br, m*320), 372/370 (59/58%, 453/451/449-Br), 306 (35%, 386/385-Br), 284/282 (14/15%, 387/385-C_6H_5CN), 264 (30%, 306-C_2H_5O).

(d) N'-(2,4-Dibromophenyl)-N'-propionylbenzothiohydrazide (70) (2.0 g) in a mixture of propionic anhydride (3 ml) and acetonitrile (3 ml) was heated at reflux for 2 h. On cooling, the solution deposited 3-(2,4-dibromophenyl)-2-(3-pentanon-2-ylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (150) (1.96 g, 93%) as yellow prisms, m.p. 182-185°. Crystallization from benzene/hexane gave material of m.p. 183-185° (Found: C, 47.49; H, 3.31; N, 5.63. $C_{19}H_{16}Br_2N_2OS$ requires C, 47.52; H, 3.36; N, 5.83%); ν_{max} 1600 (C=O), 1475, 1465, 1435, 1175, 1280, 870, 760; pmr 1.17 (t, 3H, J = 7 Hz, $\underline{CH_3}$-CH_2-), 1.55 (s, 3H, CH_3-C=), 2.52 (q, 2H, J = 7 Hz, -$\underline{CH_2}$-CH_3), 7.2-7.9 (m, 8H, arom.); m/e 482/480/478 (53/100/50%, M^+), 453/451/449 (12/22/12%, $M^+-C_2H_5$), 425/423/421 (11/18/10%, $M^+-C_3H_5O$), 401/399 (49/45%, M^+-Br, m* 355), 372/370 (98/100, 453/451/449-Br, m* 305), 320 (7%, 401/399-Br), 298/296 (9/9%, 401/399-C_6H_5CN), 291 (7%, 372/370-Br).

(e) N'-Acetyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (69) (1.9 g) in acetonitrile (10 ml) containing benzoic anhydride (5.3 g) was heated at reflux for 3 h. After cooling, 10% sodium hydroxide (60 ml) was added and the solution stirred for 2 h. The orange precipitate which separated was collected, washed with water, and dried. Column chromatography on silica gel, using benzene as eluent, followed by crystallization from acetonitrile afforded 2-acetophenonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (151) (1.66 g, 73%) as yellow prisms, m.p. 168-170° (Found: C, 51.42; H, 2.82; N, 5.35. $C_{22}H_{14}Br_2NOS$

requires C, 51.38; H, 2.74; N, 5.45%); ν_{max} 1595 (C=O), 1560, 1495, 1460, 1430, 1220, 900, 735; pmr 6.16 (s, 1H, H-C=), 7.37-7.92 (m, 13H, arom.); m/e 516/514/512 (31.4/60.0/34.3%, M^+), 499/497/495 (1.3/2.0/1.3%, M^+-OH), 435/433 (85.7/82.9%, M-Br, m* 368), 358/356 (17.7/18.0%, 435/433-C_6H_5), 330/328 (6.0/5.1%, 358/356-CO), 307/305 (4.3/4.1%), 277 (3.1%, 358/356-Br), 105 (100%, C_6H_5CO).

(f) N'-Acetyl-N'-phenyl-benzothiohydrazide (72) (1.0 g) in pyridine (10 ml) containing benzoic anhydride (4.2 g) was heated at reflux for 1 h. The brown solution was then poured into water (200 ml) containing sodium hydroxide (5 g) and the precipitate obtained upon stirring was collected. Column chromatography on silica gel, using benzene as eluent, followed by crystallization from acetonitrile afforded the 2-acetophenonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (152) (820 mg, 62%) as pale orange prisms which melted at 160-162°, resolidified and melted again at 169-170°. A sample crystallized from ethanol as short yellow needles, m.p. 170-171° (lit.[51] 170°); ν_{max} 1600 (C=O), 1560, 1540, 1490, 1460, 1425, 1530, 1220; pmr 6.70 (s, 1H, =C-H), 7.03-8.03 (m, 15H, arom.).

Mass spectrum (includes ions >2.0% and >m/e 100)

m/e	relative intensity	m/e	relative intensity
359	2.1%	340	14.6%
358	10.4%	339	54.2%
357	27.1%	323	m*
356	100.0%	281	4.2%
355	33.3%	280	12.5%
354	m*	279	45.8%

m/e	relative intensity	m/e	relative intensity
265	2.3%	145	6.5%
253	4.9%	144	47.9%
252	14.6%	135	2.1%
251	22.9%	132	4.4%
247	5.4%	131	2.1%
224	2.3%	123	2.1%
221	3.1%	122	5.0%
220	3.1%	121	20.8%
218	2.1%	120	4.8%
204	2.9%	119	2.1%
195	3.5%	117	4.2%
194	16.7%	116	12.5%
193	2.5%	110	7.1%
178	3.1%	109	16.7%
176	5.0%	108	2.5%
165	3.5%	106	7.1%
160	2.5%	105	70.8%
150	7.7%	104	16.7%
149	4.0%	103	29.2%
148	20.8%	102	7.5%
147	2.5%	74.5	m*
146	3.3%		

2-Acetonylidene-3,5-diphenyl-Δ^4-1,3,4,-thiadiazoline (129)

N'-Phenylbenzothiohydrazide (67) (1.0 g) in acetic anhydride (10 ml) was heated at reflux for 1 h. The usual workup afforded thiadiazoline (129) (820 mg, 65%) as white needles, m.p. and mixed m.p. 150-152°.

Reaction of the 2-Acetonylidene Compound (129) with Perchloric Acid

2-Acetonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (129) (200 mg) in ethanol (5 ml) containing perchloric acid (1 ml) was heated at reflux for 12 h. After being allowed to cool, the solution was poured into ether (50 ml) and left to stand for several hours. The precipitate which formed was collected and dried. This afforded 2-methyl-3,5-diphenyl-1,3,4-thiadiazolium perchlorate (94) (160 mg, 67%), m.p. 165-167° and mixed m.p. 164-166°. The mass spectrum was identical with that of an authentic sample.

Reaction of the Benzothiohydrazide (68) with Diketene

N'-(2,4-Dibromophenyl)-benzothiohydrazide (68) (1.0 g) in benzene (10 ml) containing diketene (1 ml) was heated at reflux overnight. The solvent was evaporated and the residual brown oil taken up in acetonitrile. This gave 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (702 mg, 60%) as yellow prisms, m.p. 148-154°. Successive recrystallizations gave material of m.p. and mixed m.p. 155-157°.

Attempted Preparation of 3-Methyl-1-phenyl-2-thiobenzoyl-pyrazol-5-one (146)

A solution of 3-methyl-1-phenyl-5-pyrazolone (161) (2.0 g) and thiobenzoylthioglycolic acid (2.44 g) in 50% methanol (50 ml) containing sodium hydroxide (1.0 g) was heated at reflux for 30 min. The solution was allowed to cool and then acidified with acetic acid (10 ml). The precipitate which formed was crystallized from ethanol. This afforded 3-methyl-1-phenyl-4-thiobenzoyl-pyrazol-5-one (163) (610 mg, 18%) as yellow needles, m.p. 105-107° (Found: C, 69.13; H, 4.83; N, 9.49. $C_{17}H_{14}N_2OS$ requires C, 69.36; H, 4.79; N, 9.52%); ν_{max} 1600, 1540, 1500, 1480, 1425, 980, 770, 705; pmr 1.83 (s, 3H, =C-CH_3), 7.3-8.1 (m, 10H, arom.), 14.16 (s, 1H); m/e 294 (33.9%, M^+), 293 (100%, M^+-H, m* 292), 277 (5.4%, M^+-OH), 261 (92.3%, M^+-SH), 233 (3.9%, 261-CO), 180 (3.1%), 175 (3.9%), 161(3.9%).

SECTION 5

Reactions of some Acyl Derivatives of the Anhydrobase with Phosphorus Pentasulfide

(a) 2-Acetophenonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (152) (430 mg) in xylene (50 ml) containing phosphorus pentasulfide (2.2 g) was heated at reflux for 75 min. The hot solution was decanted and the residual solid extracted with boiling xylene (50 ml). The combined extracts were washed with water (3 x 200 ml), 5% sodium hydroxide (2 x 200 ml) and again with water (2 x 200 ml). After drying the solution (sodium sulfate), the solvent was removed. Column chromatography on silica gel using benzene as eluent followed by crystallization from ethanol afforded 3,5-diphenyl-2-thioacetophenonylidene-Δ^4-1,3,4-thiadiazoline (177) (150 mg, 26%) as short orange needles, m.p. 210-212° (lit.[51] 212°); ν_{max} 1525, 1490, 1470, 1445, 1250, 775, 755, 680; pmr 7.13-8.03 (-CH and arom.).

Mass spectrum (includes ions >2.0% and >m/e 100)

m/e	relative intensity	m/e	relative intensity
374	2.1%	268	5.8%
373	4.7%	267	m*
372	13.7%	206	2.6%
371	8.9%	205	13.2%
271	6.8%	204	19.5%
270	11.6%	186	4.2%
269	63.2%	166	6.3%

m/e	relative intensity	m/e	relative intensity
155	m*	116	2.1%
150	2.5%	109	2.0%
149	2.8%	105	3.7%
135	2.1%	104	36.8%
134	3.1%	103	100.0%
128	2.3%	102	2.0%
121	11.6%		

(b) 2-Acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (3.7 g) in dry benzene (70 ml) containing phosphorus pentasulfide (4.4 g) was heated at reflux for 15 min. The suspension was filtered while hot and the remaining solid washed with boiling benzene (50 ml) The combined benzene solutions were washed with water (3 x 200 ml), 5% sodium hydroxide (2 x 300 ml) and again with water until the washings were neutral. Removal of the solvent followed by crystallization from 95% ethanol gave 3-(2,4-dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-thiadiazoline (117) (1.8 g, 46%) as yellow needles, m.p. 185-187° (Found: C, 43.77; H, 2.64; N, 5.86. $C_{18}H_{14}Br_2N_2OS$ requires C, 43.60; H, 2.58; N, 5.98%); ν_{max} 1530, 1495, 1480, 1475, 1275, 1260, 770, 765; pmr 2.70 (s, 3H, $CH_3C{=}S$), 6.60 (s, 1H, H-C=), 7.2-8.1 (m, 8H, arom.); m/e 470/468/466 (1/2/1%, M^+), 389/387 (100/99%, M^+-Br, m* 377), 367/365/363 (49/90/44%, $M^+-C_6H_5CN$), 357/355 (31/30%, 389/387-S), 308 (42%, 389/387-Br, m* 244), 302/300/298 (42/82/42%, 367/365/363-S_2H), 286/284 (18/17%, 367/365/363-Br, m* 223), 263/261/259 (11/19/11%, $C_6H_3Br_2CN$).

(c) A suspension of 2-acetophenonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (151) (750 mg) and phosphorus pentasulfide (800 mg) in dry benzene (25 ml) was heated at reflux for 30 min. This was filtered while hot and the remaining solid extracted with boiling benzene (50 ml). The combined benzene solutions were washed with water (3 x 100 ml), 5% sodium hydroxide (3 x 100 ml) and water (3 x 100 ml). Removal of the solvent followed by crystallization from chloroform/light petroleum (30-60°) afforded 3-(2,4-dibromophenyl)-5-phenyl-thioacetophenonylidene-Δ^4-1,3,4-thiadiazoline (128) (540 mg, 68%) as orange needles, m.p. and mixed m.p. 224-227°.

Reaction of the 2-Thioacetonylidene Compound (117) with Mercuric Acetate

3-(2,4-Dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (117) (1.0 g) in acetic acid (40 ml) containing mercuric acetate (750 mg) was heated at reflux for 5 min. The solution was allowed to cool, poured into water (400 ml) and the precipitate collected. Column chromatography on silica gel using benzene as eluent afforded 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (650 mg, 67%) as dark brown prisms, m.p. 148-152°. Successive recrystallizations gave material of m.p. and mixed m.p. 155-157°.

Reactions with Thioacetic Acid

(a) A suspension of N'-acetyl-N'-(2,4-dibromophenyl)-benzothiohydrazide (69) (2.0 g) in thioacetic acid (10 ml) was stirred at room temperature for 12 h. T.l.c. of the reaction mixture showed only the presence of starting material. The mixture was then heated at reflux for 45 min. Removal of the excess solvent under reduced pressure followed by column chromatography on silica gel using benzene as eluent afforded 3-(2,4-dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (117) (1.14 g, 52%), m.p. and mixed m.p. 185-187° (from 95% ethanol). Further elution gave 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (320 mg, 15%), m.p. 150-154° (from acetonitrile). Further crystallization of the latter gave material of m.p. and mixed m.p. 155-157°.

(b) Similar treatment and workup of N'-(2,4-dibromophenyl)-benzothiohydrazide (68) (5 g) in thioacetic acid (20 ml) afforded 3-(2,4-dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (117) (3.6 g, 59%), m.p. and mixed m.p. 185-187°, and 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (1.1 g, 24%), m.p. and mixed m.p. 155-157°.

(c) Similarly, N'-phenyl-benzothiohydrazide (67) (3.1 g) in thioacetic acid (15 ml) afforded 3,5-diphenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (188) (3.24 g, 78%) as orange needles, m.p. 162-163° (from ethanol) (Found: C, 65.94; H, 4.63; N, 8.80. $C_{17}H_{14}N_2S$ requires C, 65.77; H, 4.55; N, 9.03%); ν_{max} 1525, 1490, 1460, 1270, 1120, 780, 760, 690; pmr 2.67 (s, 3H, H_3C-C=), 7.01 (s, 1H, H-C=), 7.48-7.96 (m, 10H, arom.).

Mass spectrum (includes ions >2.0% and >m/e 100)

m/e	relative intensity	m/e	relative intensity
312	3.8%	201	11.4%
311	7.3%	143	11.3%
310	36.6%	142	39.4%
209	11.3%	139	m*
208	15.5%	117	2.4%
207	100.0%	104	4.2%
206	15.5%	98-97	m*
205	m*		

Further elution gave 2-acetonylidene-3,5-diphenyl-Δ^4-1,3,4-thiadiazoline (129) (200 mg, 5%), m.p. and mixed m.p. 150-152°.

(d) A suspension of 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (2.0 g) in ethanol (30 ml) containing triethylamine (1.2 ml) and thioacetic acid (0.31 ml) was heated at reflux for 2 h. After cooling, the solvent was removed and the residual red solid taken up in chloroform (50 ml). This was washed with water (3 x 50 ml) and dried (sodium sulfate). Column chromatography on silica gel, using benzene as eluent, afforded 3-(2,4-dibromophenyl)-5-phenyl-2-thioactonylidene-Δ^4-1,3,4-thiadiazoline (117) (880 mg, 48%), m.p. and mixed m.p. 185-187° (95% ethanol). A spot (t.l.c.) corresponding to 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) was observed but could not be isolated due to reaction byproducts with closely similar R_f values.

SECTION 6

Reactions of the 2-Methylthio-1,3,4-thiadiazolium Salt (99) with Nucleophiles

(a) A suspension of 3-(2,4-dibromophenyl)2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (500 mg) in water (25 ml) was stirred overnight. The strong stench of methyl mercaptan was noticed. The solid was collected and washed with water. Crystallization from ethanol afforded 3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazol-2-one (218) (200 mg, 51%), m.p. and mixed m.p. 150-152°. This was also shown to be identical (t.l.c.) with an authentic sample prepared by the method of Pawelchak[75].

(b) A suspension of 3-(2,4-dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (470 mg) in water (25 ml) containing sodium hydrosulfide (3 g) was stirred for 6 h. The solid was collected, washed with water and crystallized from ethanol. This afforded 3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazol-2-thione (100) (290 mg, 80%), m.p. and mixed m.p. 128-129°.

(c) 3-(2,4-Dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (1.5 g) in dry acetonitrile (10 ml) containing diethylmalonate (0.49 ml) and triethylamine (0.75 ml) was heated at reflux for 30 min. This was concentrated to half its original volume and left to stand in the refrigerator for 24 h. The precipitate was collected, washed with acetonitrile and crystallized from 95% ethanol. This afforded 3-(2,4-dibromophenyl)-2-(diethoxycarbonyl-methylene)-5-Phenyl-Δ^4-1,3,4-thiadiazoline (219) (720 mg, 54%) as prisms,

m.p. 175-177° (Found: C, 45.58; H, 3.24; N, 5.08. $C_{21}H_{18}Br_2N_2O_4S$ requires C, 45.50; H, 3.27; N, 5.06%); ν_{max} 1725 (C=O), 1650 (C=O), 1550, 1510, 1475, 1350, 1230, 1160; pmr 1.20 (t, 6H, $\underline{H_3C}$-CH_2-), 3.93 (m, 4H, H_3C-$\underline{CH_2}$-O), 7.2-8.0 (m, 8H, arom.); m/3 556/554/552 (18/32/18%, M^+), 511/509/507 (7.8/13/6.8%, M^+-C_2H_5O), 484/482/480 (9/15/8.3%, 511/509/507-$C_2H_4CO_2$), 475/473 (20/22%, M^+-Br), 439/437/435 (5/7.3/4.5%, 484/482/480-C_2H_5O), 412/410/408 (5.5/11.5/8.5%, 484/482/480-$C_2H_4CO_2$), 103 (100%, C_6H_5CN).

(d) 3-(2,4-Dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (1.5 g) in dry acetonitrile (10 ml) containing acetylacetone (0.31 ml) and triethylamine (0.75 ml) was heated at reflux for 30 min. This solution was concentrated to half its original volume and left in the refrigerator for 24 h. The precipitate was collected washed with acetonitrile and dried (860 mg). Crystallization from acetonitrile afforded 2-acetonylidene-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (126) (580 mg, 47%) as tan coloured prisms, m.p. 153-156°. Further crystallization gave material of m.p. and mixed m.p. 155-157°.

(e) 3-(2,4-Dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (1.5 g) in dry acetonitrile (10 ml) containing ethyl acetoacetate (0.38 ml) and triethylamine (0.75 ml) were heated at reflux for 30 min. The solution was concentrated to half its original volume and left to stand in the refrigerator for 24 h. The precipitate was collected, washed with acetonitrile and dried (910 mg). T.l.c. showed it to consist of two components and these were separated on a silica gel column using benzene as eluent. This gave, in order of elution: 3-(2,4-dibromophenyl)-2-(ethoxycarbonylmethylene)-5-phenyl-

Δ^4-1,3,4-thiadiazoline (220) (290 mg, 22%) as fluffy needles (95% ethanol) m.p. 147-148° (Found: C, 44.77; H, 2.96; N, 5.70. $C_{18}H_{14}Br_2N_2OS$ requires C, 44.83; H, 2.93; N, 5.81%); ν_{max} 1655 (C=O), 1550, 1525, 1465, 1365, 1185, 1150, 752, 675; pmr 1.25 (t, 3H, $\underline{CH_3}CH_2$-, J = 7.2 Hz), 4.20 (q, 2H, $CH_3\underline{CH_2}$-O-, H = 7.2 Hz), 4.83 (s, 1H, H-C=), 7.2-8.0 (Arom., 8H); m/e 484/482/480 (57/100/57%, M^+), 439/437/435 (11/17/9%, $M^+-C_2H_5O$), 412,410,408 (24/44/23%, 439/437/435-CO), 403/401 (79/71%, M^+-Br), 375/373 (11/11%, 403/401-C_2H_5), 358/356 (40/39%, 403/401-C_2H_5O), 322 (24%, 402/401-Br), 294 (35%, 375/373-Br); and

2-(acetylethoxycarbonyl-methylene)-3-(2,4-dibromophenyl)-5-phenyl-Δ^4-1,3,4-thiadiazoline (221) (420 mg, 29%) as prisms, m.p. 183-180° (Found: C, 46.09; H, 3.13; N, 5.22. $C_{20}H_{16}Br_2N_2O_3S$ requires C, 45.82; H, 3.08; N, 5.35%); ν_{max} 1710 (C=O), 1605 (C=O), 1470, 1435, 1320, 1225; pmr 1.26 (t, 3H, $\underline{CH_3}CH_2$-), 2.46 (s, 3H, CH_3-C=), 3.67 (m, 2H, -$\underline{CH_2}CH_3$), 7.26-8.03 (m, 8H, arom.); m/e 526/524/522 (18.2/31.8/18.2%, M^+), 511/509/507 (5.9/8.6/4.6%, M^+-CH_3), 481/479/477 (7.3/9.1/7.3%, $M^+-CH_3CH_2O$), 445/443 (50/45.5%, M^+-Br), 439/437/435 (11.4/20.9/16.4%, 481/479/477-CH_2CO), 417/415 (10/9.6%, 445/443-C_2H_4), 403/401 (100/95.5%, 445/443-CH_2CO), 358/356 (68.2/68.2, 403/401-CH_3CH_2O).

SECTION 7

Bis[3-(2,4-dibromophenyl)-5-phenyl-1,3,4-thiadiazol-2-yl]tricarbocyanine perchlorate (244)

3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g) in pyridine (10 ml) containing triethylorthoformate (1.0 ml) was heated at reflux for 45 min. The precipitate was collected, crystallized from pyridine/methanol giving bis[3-(2,4-dibromophenyl)-5-phenyl-1,3,4-thiadiazol-2-yl]-tricarbocyanine perchlorate (244) as prisms with a golden luster (740 mg, 81%), m.p. 290-295° (Found: C, 41.45; H, 2.23; N, 6.39. $C_{31}H_{19}Br_2ClN_4O_4S_2$ requires C, 40.00; H, 2.06; N, 6.02. $C_{31}H_{19}Br_2ClN_4O_4S_2 \cdot \frac{1}{2}C_5H_5N$ requires C, 41.47; H, 2.23; N, 6.46%); ν_{max} 1560, 1475, 1360, 1300, 1200, 1180, 1090, 880; λ_{max}560 (5.01). The mass spectrum confirms the presence of pyridine (m/e 79, M^+).

Bis[3-(2,4-dibromophenyl)-5-phenyl-1,3,4-thiadiazol-2-yl]-carbocyanine perchlorate (245)

(a) A suspension of 3-(2,4-dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.9 g) and 3-(2,4-dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium perchlorate (99) (2.0 g) in ethanol (40 ml) containing triethylamine (0.56 ml) was heated at reflux for 30 min. After being allowed to cool, the yellow precipitate was collected, washed with ethanol, and crystallized from pyridine/methanol. This afforded bis[3-(2,4-dibromophenyl)-5-phenyl-1,3,4-thiadiazol-2-yl]-carbocyanine perchlorate (245) (2.63 g, 79%) as yellow prisms,

m.p. >325° (Found: C, 38.44; H, 1.93; N, 6.10. $C_{29}H_{17}Br_4ClN_4O_4S_2$ requires C, 38.49; H, 1.90; N, 6.19%); ν_{max} 1515, 1490, 1470, 1450, 1280, 1100, 770; λ_{max} 427 (4.70).

(b) N'-(2,4-Dibromophenyl)-benzothiohydrazide (68) (2.0 g) and malononitrile (170 mg) in acetic acid (4 ml) containing perchloric acid (2 ml) was heated at reflux for 5 min. Upon the slow addition of water (40 ml) to the cooled suspension, the colourless precipitate (ammonium perchlorate) went into solution and a yellow gum was deposited. Trituration of the gum with water caused it to solidify. Crystallization of this solid from pryidine/methanol, gave the carbocyanine perchlorate (1.8 g, 77%) (245) as yellow prisms, m.p. >325° with an infrared spectrum identical with that already described.

3-(2,4-Dibromophenyl)-2-(3-ethylrhodanylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (246)

3-(2,4-Dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (99) (1.5 g) and 3-ethylrhodanine (440 mg) in dry acetonitrile (10 ml) containing triethylamine (0.75 ml) was heated at reflux for 20 min. The precipitate was collected and washed with ethanol; yield 1.14 g (75%), m.p. 236-240°. Crystallization from benzene/acetone gave 3-(2,4-dibromophenyl)-2-(3-ethylrhodanylidene)-5-phenyl-Δ^4-1,3,4-thiadiazoline (246) as bright yellow prisms, m.p. 240-242° (Found: C, 41.11; H, 2.19; H, 7.58. $C_{19}H_{13}Br_2N_3OS_3$ requires C, 41.10; H, 2.32; N, 7.57%); ν_{max} 1650 (C=O), 1545, 1505, 1460, 1320, 1230, 1110; pmr 1.26 (t, 3H, $\underline{CH_3}$-CH_2-, J = 7 Hz),

4.14 (q, 2H, CH_3-CH_2-, J = 7 Hz), 7.2-8.0 (m, 8H, arom.); m/e 557/555/553 (48/80/40%, M^+), 476/474 (6.7/6.7%, M^+-Br), 470/468/466 (4.5/6.7/4.5%, M^+-C_2H_5NCS), 470/468/466-Br), 361/359 (100/91%, 442/440/438-Br), 399/337/335 (25/42/22%, 442/440/438-C_6H_5CN), 295/293/291 (13/25/13%, 339/337/335-CS); λ_{max} 424 (4.70).

5-Anilinomethylene-3-ethylrhodanine

3-Ethylrhodanine (4 g) and ethyl-N-phenyl isoformimidate (4.5 g) in ethanol (5 ml) were heated under reflux for 25 min. The red solid was filtered, washed with methanol and dried. This gave the rhodanine derivative (6 g, 88%), m.p. 181-184° (lit.[76] 184-186°), which was used without further purification.

5-Acetanilidomethylene-3-ethylrhodanine (248)

5-Anilinomethylene-3-ethylrhodanine (6 g) in acetic anhydride (25 ml) containing triethylamine (3.2 ml) was heated at reflux for 10 min. The precipitate which formed on cooling was filtered off, washed with methanol, and crystallized from methanol. This afforded the acetylated derivative (248) as yellow needles (4.9 g, 71%), m.p. 90-94° and on resolidifying, 123-125° (lit.[76], 85-87° and 128-130°).

3-(2,4-Dibromophenyl)-2-[(3-ethylrhodanylidene)-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (250)

3-(2,4-Dibromophenyl)-2-methyl-5-phenyl-1,3,4-thiadiazolium perchlorate (82) (1.0 g) and 5-acetanilinomethylene-3-ethylrhodanine (248) (780 mg) in dry ethanol (20 ml) containing triethylamine (0.55 ml)

were heated at reflux for 30 min. After cooling, the precipitate was filtered off, washed with ethanol, and dried (940 mg, 83%), m.p. 240-244°. Crystallization from pyridine/methanol afforded 3-(2,4-dibromophenyl)-2-[(3-ethylrhodanylidene)-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (250) as red prisms, m.p. 242-244° (Found: C, 43.39; H, 2.47; N, 7.14. $C_{21}H_{15}Br_2N_3OS_3$ requires C, 43.39; H, 2.60; N, 7.23%); ν_{max} 1695 (C=O), 1575, 1560, 1525, 1475, 1320, 1213, 1130; m/e 583/581/579 (32/53/26%, M^+), 468/466/464 (10/17/9%, M^+-$CONH_3CS$), 387/385 (15/15%, 468/466/464-Br), 243/242 (8/7%, 387/385-CS), 234/233/232 (10/16/8%, (468/466/464)2+), 203 (24%, $C_6H_5CSCC_2H_2CS$), 121 (37%, C_6H_5CS), 103 (100%, C_6H_5CN); λ_{max} 517 (4.79).

3-(2,4-Dibromophenyl)-2-[2-(3-ethylrhodanylidene)-1-methyl-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (251)

3-(2,4-Dibromophenyl)-2-ethyl-5-phenyl-1,3,4-thiadiazolium perchlorate (83) (1.0 g) and 5- acetanilinomethylene-3-ethylrhodanine (248) (700 mg) in dry ethanol (20 ml) containing triethylamine (0.53 ml) was heated at reflux for 2 h. After cooling, the precipitate was collected, washed with ethanol and crystallized from pyridine/methanol. This gave 3-(2,4-dibromophenyl)-2-[2-(3-ethylrhodanylidene)-1- methyl-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (251) (630 mg, 55%) as red prisms, m.p. 213-215° (Found: C, 44.89; H, 2.93; N, 6.91. $C_{22}H_{17}Br_2N_3OS_3$ requires C, 44.38; H, 2.88; N, 7.06%); ν_{max} 1690 (C=O), 1560, 1501, 1490, 1470, 1305, 1240, 1125; m/e 597/595/593 (28.3/46.7/21.7%, M^+), 516/515 (3.7/3.0, M^+-Br), 494/492/490 (1.2/1.7/0.9%, M^+-C_6H_5CN),

482/480/478 (1.5/2.7/1.5%, M^+-$CONC_2H_5CS$), 481/479/477 (1.5/1.8/1.2%, 482/480/478-H), 453/451/449 (5.0/7.5/4.2%), 439/437/435 (1.2/1.7/1.2%), 103 (100%, C_6H_5CN); λ_{max} 519 (4.74).

3-(2,4-Dibromophenyl)-2-(2-methylthiopropenyl)-5-phenyl-1,3,4-thiadiazolium iodide (253)

3-(2,4-Dibromophenyl)-5-phenyl-2-thioacetonylidene-Δ^4-1,3,4-thiadiazoline (117) (1.28 g) in dry benzene (40 ml) containing methyl iodide (1.6 ml) was heated at reflux for 1 h. 3-(2,4-Dibromophenyl)-2-(2-methylthiopropenyl)-5-phenyl-1,3,4-thiadiazolium iodide (253) (1.6 g, 96%) precipitated as an orange solid which was used without further purification, m.p. 185-190° (decomp.).

3-(2,4-Dibromophenyl)-2-[2-(3-ethylrhodanylidene)-2-methyl-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (252)

3-(2,4-Dibromophenyl)-2-(2-methylthiopropenyl)-5-phenyl-1,3,4-thiadiazolium iodide (253) (1.0 g) and 3-ethylrhodanine (320 mg) in dry ethanol (20 ml) containing triethylamine (0.45 ml) was heated at reflux for 1 h. After cooling, the precipitate was collected, washed with ethanol and crystallized from pyridine/methanol. This afforded 3-(2,4-dibromophenyl)-2-[2-(3-ethylrhodanylidene)-2-methyl-ethylidene]-5-phenyl-Δ^4-1,3,4-thiadiazoline (252) (810 mg, 83%) as red prisms, m.p. 247-249° (Found: C, 44.82; H, 2.89; N, 6.82. $C_{22}H_{17}Br_2N_3OS_3$ requires C, 44.38; H, 2.88; N, 7.06%); ν_{max} 1650 (C=O), 1510, 1490, 1465, 1440, 1270, 1240, 1140; m/e 597/595/593 (21.7/32.6/19.6%, M^+), 416/414 (3.9/3.3%, M^+-Br), 415/413 (7.6/5.9%, M^+-HBr), 494/492/490

(1.1/1.8/1.1, $M^+-C_6H_5CN$), 482/480/478 (4.8/7.8/4.4, $M^+-CONC_2H_5CS$), 453/451/449 (1.7/3.0/2.0%), 439/437/435 (1.1/1.7/1.1%), 103 (100%, C_6H_5CN); λ_{max} 510 (4.65).

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